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ISOLATION OF ECHO VIRUS TYPE 9 FROM CEREBROSPINAL FLUIDS

By ANNELOISE GODTFREDSEN and HERDIS VON MAGNUS

In the fall of 1956 the incidence of lymphocytic meningitis was rather high in Denmark while only few cases of polio, paralytic or nonparalytic, were observed. Echo virus type 9 was isolated in many instances from stool specimens from patients with lymphocytic meningitis (data to be published).

While ordinarily only stool samples from such cases have been submitted to this laboratory for virus study, cerebrospinal fluids were also received from some of these patients. It was found that echo virus could be recovered from this material with a surprisingly high frequency.

For this reason it seemed of interest to carry out a more extensive virus study on cerebrospinal fluids from patients with symptoms of involvement of the central nervous system. Such fluids were made available by the Diagnostic Department of this institute which daily receives an appreciable number of cerebrospinal fluids for bacteriological examination. Most often these samples are collected during the acute stage of a febrile illness from patients with symptoms from the central nervous system.

During a 7 week period from October 30 through December 17, 1956, all cerebrospinal fluids submitted for bacteriological examination were also studied by virological methods when the amount of fluid available was sufficient. Altogether a total of 147 spinal fluids was studied in tissue culture for the presence of echo-, polio- and Coxsackie viruses.*)

METHODS

Tissue Cultures.

Roller tube cultures of trypsinized monkey kidney cells were employed. For preparation of the

*) We are indebted to Dr. Kirsten Rosendahl of the Diagnostic Department of this institute for her help in collecting material.

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tubes the method described by Younger (1) was used with some modification (2).

The nutrient medium before inoculation was 0.5 per cent lactalbuminhydrolyzate in Hank's solution with 2 per cent horse serum. Prior to inoculation this medium was replaced by 1.8 ml of bovine amniotic fluid. All media contained penicillin (100 u/ml) and streptomycin (0.1 mg/ml).

Technique of virus isolation in roller tubes.

To each of 3 roller tubes 0.2 ml of spinal fluid was added. Three tubes containing 1.8 ml of bovine amniotic fluid and serving as tissue controls were inoculated with 0.2 ml of bovine amniotic fluid. After inoculation the tubes were placed in roller drums at 37° C and examined for cytopathic changes 5, 9, and 14 days after inoculation. Cultures remaining normal for 14 days were considered negative and discarded. Culture fluid from all tubes showing cytopathic changes were harvested for further study.

Of a total of 147 spinal fluids examined in tissue cultures, 21 induced cytopathic lesions.

Repetition of the test was carried out on all positive specimens if the amount of cerebrospinal fluid was sufficient (13 out of 21). Virus was reisolated from all these fluids except one (patient No. 1066).

Examination of cytopathogenic agents isolated from spinal fluids.

Infectivity titrations: Fluids from cultures showing cytopathic changes were titrated by inoculating serial tenfold dilutions of the fluid medium in 0.2 ml amounts into groups of 5 tissue culture tubes. The tests were read after 7 days, and end points were calculated by Kärbers method (3) and expressed as 50 per cent cytopathogenic doses. The results of the infectivity titrations of first passage fluids are shown in Table 1. The titres were found to vary from 10^{3.7} to 10^{7.5}.

Table I.
Results of inoculation of spinal fluids into monkey kidney tissue cultures and into newborn mice.

Patient No.	Inoculation of spinal fluid into tissue cultures	Titer of first passage tissue culture fluid	Inoculation of spinal fluid into newborn mice	Inoculation of tissue culture virus into newborn mice
1015	+	6.3	—	—
1023	+	5.3	—	—
1029	+	6.5	—	+
1032	+	6.3	n.d.	+
1037	+	6.3	n.d.	+
1040	+	6.9	n.d.	—
1046	+	5.5	n.d.	+
1050	+	7.5	—	—
1065	+	6.3	—	—
1066	+	6.5	—	+
1071	+	6.5	—	+
1114	+	6.7	—	—
1145	+	5.7	n.d.	+
1148	+	6.5	—	—
1198	+	5.1	—	—
1200	+	4.3	—	+
1213	+	3.7	n.d.	+
1234	+	6.7	n.d.	—
1236	+	6.7	n.d.	+
1287	+	6.7	—	—
1310	+	3.7	n.d.	—

+ means virus recovered
— means virus not recovered
n.d. means not done.

Neutralization tests.

Polio antisera: Polio hyperimmune sera were prepared in Rhesus monkeys, the Mahoney, MEF-1 and Saukett strains being used. The animals were inoculated intramuscularly 4 times at biweekly intervals with 2 ml of a mixture of equal parts of virus and adjuvant (1 part Alarcel plus 9 parts of Bayol). The virus consisted of infected fluid from monkey kidney tissue cultures.

All sera thus prepared had titres of more than 1000 against 100 TCD₅₀ of the homologous virus strain and were used in a final dilution of 1:200.

Echo antisera: Strains of echo virus types 1 through 14 were kindly supplied by Dr. Albert B. Sabin. Two or three passages were carried out with each strain in trypsinized monkey kidney cells, and infected tissue culture fluid from 2nd or 3rd passage was used for hyperimmunization of rabbits.

The animals were inoculated intravenously and received 4 injections of 1 ml at weekly intervals. The animals were bled by heart puncture 1 week after the last injection.

Each serum was titrated for content of neutralizing antibodies against the homologous virus strain.

Two-fold dilutions of serum were prepared in physiological saline and mixed with equal amounts of virus-containing tissue culture fluid containing approximately 200 TCD₅₀ per 0.2 ml. The virus-serum mixtures were kept for 1 hour at room temperature and 0.2 ml of each mixture were subsequently inoculated into each of 2 roller

tubes. The cultures were placed in roller drums at 37° C and read 7 days after inoculation.

Serum titres were expressed as the reciprocal of the highest final dilution of serum protecting 50 per cent of the cells and were found to vary from 360 to 3000.

All hyperimmune sera were also tested for content of neutralizing antibodies against the heterologous echo viruses, each serum being used in a final dilution corresponding to approximately 20 units of antibody against the homologous virus. Seven sera, namely echo antiserum types 3, 6, 7, 8, 9, 11 and 12 were found to be type specific. The remaining 7 sera, however, were found to contain neutralizing antibodies, not only against the homologous virus, but also against one or more heterologous virus strains. Particularly striking was a very close relationship between types 1 and 13 (unpublished data).

Neutralization tests with polio hyperimmune monkey sera.

All agents isolated were examined in neutralization tests with a pool of poliomyelitis hyperimmune sera types I, II and III, each serum being used in a final dilution of 1:200.

None of the agents was found to be neutralized by poliomyelitis hyperimmune sera.

Inoculation of suckling mice.

Twelve out of the 21 cerebrospinal fluids which induced cytopathic changes in monkey kidney tissue cultures were also inoculated into newborn mice. An inoculum of 0.04 ml was used, the inoculum being divided between the intracerebral and intraperitoneal routes. The mice were observed daily for 11 days. None of the animals showed any symptoms (Table I).

First tissue culture passage material of all 21 agents isolated was injected into newborn mice by the technic described above. The mice were observed daily for 11 days and carcasses from mice developing paralysis were harvested. If the mice did not become paralysed using first passage material, further passages of the agent were carried out in tissue culture, and the inoculation of newborn mice was repeated with 5th tissue culture passage material.

It will be seen from Table I that first tissue culture passage fluid of 10 of the 21 agents isolated produced paralysis in suckling mice. The remaining 11 agents were not pathogenic for suckling mice even after 5 passages in tissue culture.

Neutralization tests with echo antisera.

Three of the isolated agents were examined in neutralization tests against each of the 14 echo antisera prepared as previously described in this paper.

Tissue culture fluid containing approximately 200 TCD₅₀ of virus per 0.2 ml was mixed with

equal amounts of each antiserum so diluted that the final virus-serum mixture contained approximately 20 units of antibody against the homologous virus. After incubation at room temperature for one hour, the mixtures were inoculated into roller tubes, an inoculum of 0.2 ml being used. The tubes were read 3, 5 and 7 days after inoculation.

All three agents were neutralized by echo antiserum type 9 and not by any of the other echo antisera. Consequently, the remaining 18 agents were tested only against echo antiserum type 9. All the strains were found to be neutralized by this serum.

For further confirmation, all 21 agents were retested in neutralization tests with echo antiserum type 9 supplied by Dr. Albert B. Sabin. This serum was used in a final dilution of 1:100, and approximately 100 TCD₅₀ of each virus strain were employed in the test. It was found that all agents were neutralized by this serum.

Serological studies on paired sera from the patients.

Acute and convalescent phase sera were available from 14 of the 21 patient from whom cytopathogenic agents were recovered from the cerebrospinal fluid. The sera from each patient were tested for neutralizing antibodies against the virus strain isolated from the patient. The results are shown in Table II.

Table II.
Virus neutralization tests.
Paired sera from patients tested against the homologous strain of virus isolated from the cerebrospinal fluid.

Patient No.	Day of illness		Serum titer	
	acute	conv.	acute	conv.
1015	3	29	<2	23
1037	6	22	16	1024
1040	6	21	128	1024
1046	8	22	256	256
1050	4	19	<4	23
1065	4	22	<4	64
1066	5	24	8	64
1114	5	16	11	32
1145	6	24	<2	8
1200	2	19	<2	256
1213	1	19	<2	4
1236	2	17	<2	64
1287	6	16	2	256
1310	5	19	2	11

It will be seen that the tests on the paired sera from 13 of the patients showed a rise in neutralizing antibodies while serum samples from one patient (No. 1046) showed no rise in antibody level, the titer being 256 in both samples.

DISCUSSION

During the fall of 1956, a number of stool specimens from patients with lymphocytic meningitis was examined in our laboratory for presence of

virus. It was found that in many instances echo virus type 9 could be isolated from the stools of these patients. Also, examination of paired sera from the patients regularly showed a rise in antibody titer against the homologous strain of virus (data to be published).

However, it has been shown that echo viruses may be recovered from stool samples from a rather high percentage of apparently healthy children (4, 5). This observation indicates that these viruses are commonly present in the intestinal tract. Consequently, isolation of echo virus strains from stool specimens — even when correlated with a demonstration of an increase in antibody titer — is not in itself sufficient evidence for establishing etiological relations.

Table III.
Occurrence of echo virus type 9 in spinal fluids from different groups of patients.

Clinical diagnosis on admission to hospital	Total number examined	Total positive
Meningitis, aparytic polio	104	21
Other illnesses	29	0
No information given	14	0
Total	147	21

On this background the isolation of echo virus type 9 from the spinal fluids of patients with meningitis seems of interest. As shown in Table III, echo virus type 9 was recovered from 21 patients out of a total of 104 admitted to the hospital under a diagnosis of meningitis or aparytic polio. In contrast, no virus was recovered from 29 patients suffering from other diseases. These results strongly suggest that the illness of the 21 patients was in fact caused by echo virus type 9.

The age of the patients from whom virus was isolated from the spinal fluid varied from 3 to 32 years. No particular age distribution was noticeable.

Isolation of echo virus type 9 from cerebrospinal fluids from patients with aseptic meningitis has recently been reported by other workers (6, 7, 8), and also other types of echo viruses (types 4 and 6) have been recovered from cerebrospinal fluids from patients with aseptic meningitis (6, 10).

It is of interest that 10 of the strains isolated in our laboratory were found to be pathogenic for newborn mice after one passage in tissue culture. This affinity for mice indicates a relationship between these echo 9 strains and the Coxsackie group of viruses. Similar observations have been made in other laboratories (6, 7, 9). The 11 remaining strains were not pathogenic for newborn mice even after 5 passages in tissue culture.

At present, no explanation for this difference in the pathogenicity of the strains can be offered. The observation indicates, however, that the inherent biological properties may vary from one strain to another, even among strains belonging to the same sero-type.

SUMMARY

In the fall of 1956, a total of 147 cerebrospinal fluids from hospitalized patients with a variety of symptoms of the central nervous system were examined by inoculation of monolayer monkey kidney tissue cultures. Virus was isolated from 21 cerebrospinal fluids. All the positive samples were derived from patients admitted to the hospital under a diagnosis of meningitis or aparthic poliomyelitis.

All 21 agents isolated were neutralized by echo antiserum type 9.

First tissue culture passage of 10 of these strains was able to produce paralysis in newborn mice, while the remaining 11 strains were non-pathogenic for newborn mice even after 5 passages in tissue culture.

Serological studies on acute and convalescent phase serum from 14 patients from whom paired sera were obtained revealed an increase in

neutralizing antibody titer in 13 instances. In one case the antibody level was high and identical in the 2 serum samples obtained.

The reported findings strongly suggest that echo virus type 9 has been the etiological factor in cases of lymphocytic meningitis in Denmark in 1956.

References:

- 1) Youngner, J. S.: Proc. Soc. Exper. Biol. and Med. 1954, 85: 202.
- 2) von Magnus, P., K. Birkum Petersen, V. Bech, Inger Petersen & Herdis von Magnus: Dan. Med. Bull. 1955, 2: 236.
- 3) Kärber, G.: Arch. f. Exper. Path. u. Pharmacol. 1931, 162: 480.
- 4) Honig, E. I., J. L. Melnick et al.: J. Exper. Med. 1956, 103: 247—262.
- 5) Ramos-Alvarez, M. & A. B. Sabin: Proc. Soc. Exper. Biol. Med. 1954, 87: 655.
- 6) Johnsson, T.: Lancet 1957, 1: 590.
- 7) Boissard, G. P. B., L. J. Stokes, A. D. Macrae & F. O. MacCallum: Lancet 1957, 1: 500.
- 8) Nihoul, E. & L. Quersin-Thiry: Lancet 1957, 1: 269.
- 9) Melnick, J. L.: Proc. Soc. Exper. Biol. Med. 1957, 94: 656.
- 10) Karzon, D. T., A. L. Barron et al.: JAMA 1956, 162: 1298.

ISOLATION OF ECHO VIRUS FROM TWO CASES OF "MINOR ILLNESS" IN ADULTS

By KNUD BIRKUM PETERSEN

Mild febrile diseases of unknown etiology are widespread all over the world. Usually the diseases are characterized only by fever and signs of general intoxication (headache, muscle pains and malaise), but more or less pronounced signs of involvement of the central nervous system, the respiratory or the gastro-intestinal tracts may be present. Such sporadic illnesses are frequently diagnosed as "influenza" in spite of the fact that viruses of the influenza group very seldom seem to be involved. There is, however, reason to believe that a large proportion of these diseases must be caused by viruses.

The present paper describes two cases of minor illness in adults from whom virus isolation was attempted during the acute phase of the disease. Echo viruses were isolated from both cases, and both patients developed antibodies against the isolated agents during their convalescence.

CASE HISTORIES

I: A divorced woman (bank clerk), age 25, fell sick on September 25, 1956. Her main complaints were:

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headache, chills, slight dizziness and generalized muscle pain, particularly in the back. The temperature at the onset was 39.5° C. The fever lasted for about one week and showed a lytic decrease. The muscle pain disappeared after two to three days. There were no indications that the respiratory tract, the central nervous system or the gastro-intestinal system were involved. On clinical examination some facial congestion was noted.

During the week preceding the appearance of the disease the 2 year-old daughter of the patient had had an illness characterized primarily by catarrhal symptoms, fever and vomiting. These symptoms had completely subsided one day prior to the onset of the mother's illness.

No similar cases were known to have occurred among the immediate contacts of these two individuals.

II: A married woman (housewife), age 31, fell sick on October 6, 1956. She complained of headache, chills, slight vertigo, generalized muscle pains and some nausea. The temperature varied between 37° C and 38° C during the first two days and rose to 39° C on the third day. The fever persisted for approximately one week, decreasing slowly during that time. There was no indication of involvement of the central nervous system nor were there diarrhoea or other gastro-

intestinal symptoms. On clinical examination some facial congestion and moderate signs of inflammation of the fauces were observed. The tonsils were not enlarged.

Eight days before the onset of clinical symptoms of this patient, her 2 year-old daughter had had a febrile illness without any other symptoms. The fever lasted for only 2 days.

No similar cases were known to have occurred among the immediate contacts of these two individuals.

VIRUS ISOLATION

Material and methods: Throat washings, throat swabs and faeces were examined for the presence of virus.

Throat washings: Were obtained by asking the patient to gargle with 15 ml of a 5 per cent solution of Bacto tryptose "Difco" (5 times concentrated) in distilled water to which 100 U of penicillin per ml had been added. After collection the fluid was immediately frozen in CO₂-ice.

Throat swabs: Material was collected on wooden sticks with sterile cotton which immediately afterwards were immersed in 1.5 ml of the Bacto tryptose solution mentioned above. This sample was likewise placed in CO₂-ice.

Faeces: Daily specimens were collected for 3 days early in the disease.

Each sample thus obtained was examined for the presence of virus by inoculating tissue culture tubes of HeLa cells and of monkey kidney cells. The throat washings and the throat swab material were thawed and inoculated without any further treatment. Faeces were used as a 10 per cent suspension in ion-exchange water containing 100 U penicillin and 100 U streptomycin per ml. The faeces suspensions were also inoculated into litters of new born mice (0—1 day old).

The monkey kidney cell cultures were prepared by a modification of Youngner's method (1) previously described (2). Each tube contained 1.8 ml of Medium 199 with 100 U of penicillin and 100 U of streptomycin.

The HeLa cell cultures were prepared according to Syvertsen et al. (3) and contained 1.8 ml Medium 199 with 2 per cent rabbit serum and 2 per cent Bacto tryptose "Difco" (5 times concentrated). In some experiments cultures of human amniotic cells were also employed. These cultures were prepared by the method described by La helle (4). The maintenance medium was the same as that used for the HeLa cultures.

Results:

Cytopathic changes developed in the monkey kidney cell cultures inoculated with material from both patients. Two to three days after inoculation the cells became rounded and condensed, and on the 5th day the cells were usually completely destroyed (Fig. 2). After 2-5 passages in monkey kidney cells the titer of both agents

was between 10^{-6.5} and 10^{-7.5}. The changes were similar to those caused by polio virus.

Table I.
Virus Isolation and Serological Findings.

Patient No.	Virus Isolation			Serum Neutralization Tests		
	throat wash- ing	throat swab	faeces § 1 2 3	serum	strain case 1	strain case 2
1	+	0	+ 0 0	acute conval.	<4 *) 48	<4 96
2	+	+	+ + +	acute conval.	<4 48	<4 48

§) Faeces samples were collected on three consecutive days early in the disease.

*) Reciprocal of final serum dilution protecting 50 per cent of the cells against 1000 TC₅₀ of virus.

As shown in Table I, virus was isolated both from throat washings and from faeces of both patients. From patient No. 2 virus was recovered also from throat swabs and from all three samples of faeces, whereas from patient No. 1 virus was isolated only from the throat washings and from the first stool sample collected on the fourth day of the illness.

No changes were observed in HeLa cells even after continued passage in these cells. In human amniotic cells, however, cytopathic changes occurred in tubes inoculated with virus from infected monkey kidney cultures (Fig. 4). The changes were very similar in the two last-mentioned cell types.

IDENTIFICATION OF THE ISOLATED AGENTS

In preliminary studies the relationship of the isolated agents to a number of known viruses could be excluded: They did not belong to the influenza group of viruses as they did not agglutinate chicken red cells, did not multiply in chick embryos and did not cause clinical disease or antibody production in ferrets after intranasal inoculation. Their belonging to the Coxsackie group of viruses could also be excluded, as neither the faeces suspensions nor the tissue culture fluid from later tissue culture passages produced any disease in newborn mice. They were not adeno viruses, since they could not be grown in HeLa cell cultures, and because they did not fix complement in the presence of hyperimmune rabbit sera against adeno viruses. Finally, they were not related to polio viruses since they were not neutralized by a pool of type I, II and III polio antiserum.

Typing of the agents: Hyperimmune sera against the isolated agents from each of the patients were prepared by four semi-weekly intravenous injections of 1 ml of monkey kidney culture passage into two rabbits. The hyperimmune serum thus obtained had a titer of 1:192 against 100 tissue

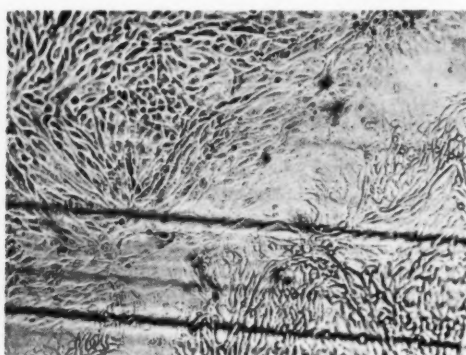


Fig. 1.

Outgrowth of normal epithelial cells in an uninoculated monkey kidney tissue culture.

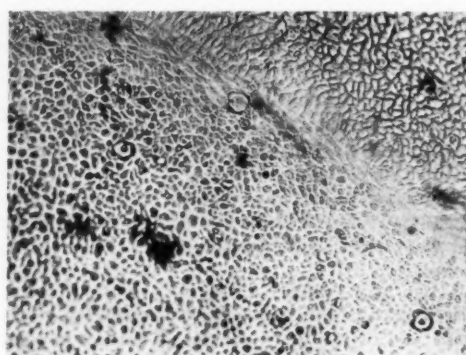


Fig. 3.

Uninoculated culture of trypsinized human amniotic tissue.

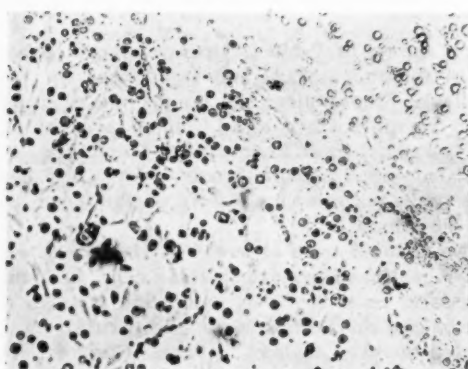


Fig. 2.

Cytopathic manifestations in monkey kidney tissue cultures inoculated with the isolated echo type 9 virus.

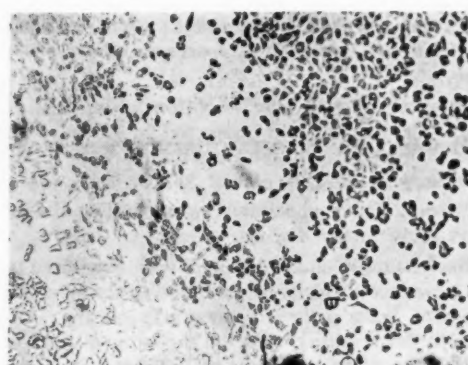


Fig. 4.

Cytopathic manifestations in human amniotic tissue inoculated with the isolated echo type 9 virus.

culture infective doses TC_{50} of the isolated agents. When tested against the echo viruses*) type 1—14, these hyperimmune sera were found to neutralize echo virus type 9 specifically. Also echo type 9 serum diluted to contain 20 neutralizing doses completely neutralized 100 TC_{50} of both isolated agents.

SERUM ANTIBODY STUDIES

Acute- and convalescent-phase sera from each of the patients were tested in monkey kidney culture tubes for neutralizing capacity. The acute phase sera contained no detectable antibodies against the two isolated agents, whereas convalescent serum from both patients diluted 1:48 or more neutralized 1000 tissue culture doses of the homologous as well as the heterologous strain.

The paired sera were also tested in complement fixation tests against antigens of influenza A, B, C and adeno viruses. Positive reactions were obtained with sera from both patients with influenza C- and with adeno virus antigens, but in no case

did the serological examination show any increase in complement fixing antibodies against these viruses.

DISCUSSION

From several points of view influenza-like cases of "Minor Illness" play an important role. The over-all loss in labour hours due to these conditions inflicts considerable economic damage on society. The individual patient also frequently suffers economically, and although the course of the illness is usually mild it may cause great inconvenience. For the general practitioners these diseases present a vexing problem because of their insusceptibility to specific therapy and the difficulties involved in the clinical diagnosis.

A large number of such minor illnesses are probably caused by viruses, but precise knowledge concerning the importance of viral agents in these conditions is still limited. For this reason a study on the etiological role of viruses in "Minor Illnesses" is at present being carried out in this laboratory.

This paper describes two cases of "Minor Illness" in adults. Both patients suffered from an

*) Echo virus and specific type sera were kindly supplied by Dr. Albert B. Sabin, Cincinnati.

acute disease with a temperature of about 39° C. The fever decreased slowly, normal temperature level being reached within a week. The main complaints were: headache, slight dizziness and generalized muscle pains.

There were no symptoms from the respiratory or the gastrointestinal tracts and there was no indication of meningitis. From both patients echo virus type 9 was isolated from throat washings and from faeces, and neutralizing antibodies against these agents developed during convalescence. On the basis of these findings it is suggested that the etiologic agent of the disease was echo virus type 9.

Our knowledge about the importance of echo viruses for diseases in humans is rapidly increasing. These viruses were first recovered from healthy children (5-7), but during the last year ample evidence has been presented that echo viruses types 4, 6 and 9 have been the etiological factors in epidemics of aseptic meningitis (8-14). In a recent study of such an epidemic which occurred in Switzerland and involved about 150 cases of infection with echo virus type 9, Baumann et al. (14) observed that only 20 per cent of the patients showed the typical picture of an aseptic meningitis. The remaining 80 per cent of the cases suffered only a mild influenza-like disease with symptoms very similar to those of the two patients described in this paper.

Epidemiologically, it is of interest to note that the Swiss cases were recognized during an epidemic of meningitis, whereas the two patients studied in the present work represent sporadic cases observed in a period when meningitis was not epidemic. The fact that both patients during the week preceeding their illness had been in close contact with a small child suffering from a short-lasting, non-characteristic febrile disease suggests a possible source of the infection, but unfortunately the etiology of the disease in the children was not established. Obviously, more studies are needed to reveal whether or not echo type 9 is to a large extent responsible for sporadic cases of "Minor Illness".

Studies on the antibody content in various pools of locally produced gammaglobulin have

shown that these do not contain neutralizing antibodies against echo virus type 9. This observation might indicate that a large proportion of the Danish population does not possess humoral antibodies against this virus.

SUMMARY

During a study on the etiology of minor febrile diseases, echo virus type 9 was recovered from the throat and from the faeces of two adult patients during the acute stage of the disease.

Both patients developed specific antibodies during convalescence against the isolated agents.

The findings are discussed, and it is suggested that echo virus type 9 was responsible for the disease in both patients.

The author wishes to express his appreciation to Dr. K. B. Rasmussen, Copenhagen, for permission to examine his patients.

References:

- 1) Youngner, J. S.: Proc. Soc. Exper. Biol. & Med. 1954, 85: 202.
- 2) von Magnus, P., K. Birkum Petersen, V. Bech, Inger Petersen & Herdis von Magnus: Dan. Med. Bull. 1955, 2: 236.
- 3) Syverton, J. T., W. Scherer & P. M. Elwood: Lab. Clin. Med. 1954, 43: 286.
- 4) Lahelle, O.: Acta path. microbiol. Scandinav. 1956, 39: 338.
- 5) Ramos-Alvarez, M. & A. B. Sabin: Proc. Soc. Exper. Biol. & Med. 1954, 87: 655.
- 6) Ramos-Alvarez, M. & A. B. Sabin: Am. J. Pub. Health 1956, 46: 295.
- 7) Hanig, E. I., J. Melnick, P. Isacson, R. Parr, I. L. Myers & M. Walton: J. Exper. Med. 1956, 103: 261.
- 8) Karzon, D. T., A. L. Barron, W. Winkelstein & S. Cohen: JAMA 1957, 162: 1298.
- 9) Davis, D. C. & J. L. Melnick: Proc. Soc. Exper. Biol. & Med. 1956, 92: 839.
- 10) Johnsson, T.: Lancet 1957, 1: 590.
- 11) Godtfredsen, Annelise & Herdis von Magnus: Isolation of echo virus type 9 from cerebrospinal fluid. Dan. Med. Bull. 1957, 4: 233.
- 12) Nihoul, E. & L. Quersin-Thiry: Lancet 1957, 1: 269.
- 13) Boissard, G. P. B., L. J. Stokes, A. D. Macrae & F. O. MacCallum: Lancet 1957, 1: 500.
- 14) Baumann, Th., M. Barben, R. Marti, A. Hassler & U. Krech: Schweiz. Med. Wschr. 1957, 87: 307.

THROMBOSIS OF THE INTERNAL CAROTID ARTERY VERIFIED BY ARTERIOGRAPHY

By HANS-HENRIK JACOBSEN and ERIK SKINHØJ

Judging from the number of cases published, thrombosis of the carotid artery appears to be a condition which occurs with greatly increasing frequency.

In 1951, the total number of published clinical cases was 107, the largest series described by a single author being 11 cases (9). Since then, the number has increased significantly, and from 1956 a single team has published personal experience concerning 70 verified cases (21).

This apparent increase in frequency is, however, primarily an expression of the improved methods of diagnosis and particularly an expression of the more extensive employment of arteriography. Without arteriography, very few of the clinical forms of the manifestation of carotid thrombosis can be recognized as cases of extracranial thrombosis, and without special technique for evisceration, ordinary routine autopsy does not render information concerning the conditions in the extracranial course of the carotid arteries. The few more comprehensive autopsy materials of non-selected patients, in which attention has been directed towards the carotid arteries and which thus should render information concerning the actual incidence of the condition, distinctly suggest, however, that a genuine increase in frequency has taken place. In his material of autopsies, Chiaris found in 1905 an incidence of occlusion of the carotid arteries of 2 per cent (corrected by exclusion of the children in the material so that the considerably greater mortality rate in children at that time will not compromise comparison with more recent materials).

In 1942 Hultquist found 4.4 per cent and in 1954 Fisher found 6.5 per cent cases with total occlusion of one or both carotid arteries, while in further 3 per cent of Fisher's material, marked arteriosclerotic-thrombotic narrowing of the carotid arteries was encountered.

The authors of the present paper consider publication of their 27 cases justifiable, because a disease with an increasing incidence is concerned, because the disease is diagnosed far less frequently than it actually occurs and, finally, because both surgically and medically (thrombectomy, operations for anastomosis, and treatment with anticoagulants) the prospects of treatment have assumed new horizons.

From the Department of Radiology, Bispebjerg Hospital, Copenhagen (Head: Kjeld Andersen) and the Department of Neurology, Municipal Hospital, Copenhagen (Head: T. Fog).

MATERIAL

The authors' material originates from the Department of Neurolog, Municipal Hospital, Copenhagen (14 patients), the Department of Neurosurgery, Bispebjerg Hospital, Copenhagen (11 patients) and the Neuro-Medical Department, University Hospital, Copenhagen (2 patients) during the years 1953—56.

The tendency for the number of diagnosed cases of thrombosis of the carotid artery to increase is reflected also in this brief period, as 3 of the patients were admitted to hospital in 1953, 4 in 1954, 10 in 1955 and 10 in the first 6 months of 1956. These figures, however, render no information whatsoever as regards the incidence of the disease in the population.

SEX AND AGE DISTRIBUTION

Twenty-one of the patients were males and only 6 females. This significant preponderance of males is found in nearly all records and deviates strikingly from the sex distribution in a material of cases of apoplexy where the relationship is 40 per cent males compared with 60 per cent females. (When comparison is made with the conditions in cerebral apoplexy, both here and elsewhere in the present paper, a material of 1,000 cases of cerebral apoplexy from Frederiksberg (3) is employed).

The average age on admission in the authors' series of cases was 54 years, the youngest patient being 33 years and the oldest 66 years of age. This age distribution differs considerably from the ordinary apoplexy material in which the average age is 70 years. This age difference may be partially an artefact due to the fact that a patient aged 54 years is more readily hospitalized in a neurological department than is a patient of 70 years, should neurological symptoms occur.

PREDISPOSING AND PROVOKING FACTORS

In 12 out of the 27 patients, no conditions were found either in the case history or in the clinical investigation which could reasonably be suspected to be predisposing.

In 8 patients arteriosclerosis and/or arterial hypertension were found. In 4 patients considerable abuse of alcohol had taken place. In 2 patients generalized vascular disease (one case of pulseless disease and one case of Buerger's disease) was encountered. Diabetes mellitus was present in one case.



Fig. 2.
Occlusion of the internal carotid artery.
The knob filled with radio-opaque medium at the tip of the needle is all that can be discerned of the cervical part of the internal carotid artery.
The branches of the external carotid artery have filled, and some radio-opaque medium has flowed retrogradely via the ophthalmic artery into the carotid syphon and the anterior cerebral artery.

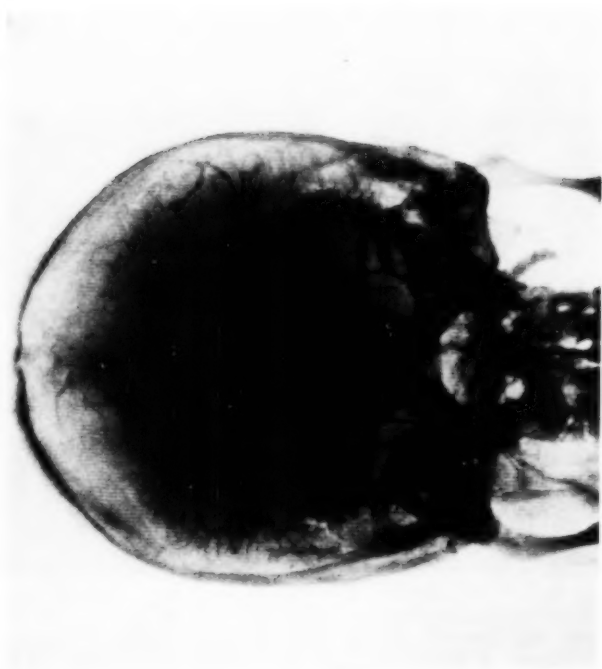


Fig. 1.
This normal arteriogram illustrates the anastomosis between the two hemispheres via the anterior communicating artery.
During the injection into the right carotid artery, the left carotid was compressed so that the pressure in the left hemisphere was lowered and the radio-opaque medium could flow over into the left cerebral arteries.

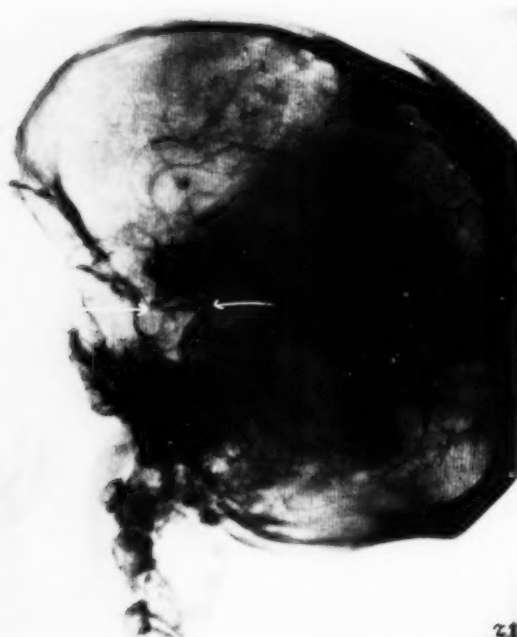


Fig. 3.

This patient showed clinical signs of thrombosis of the left internal carotid artery.

On arteriography the vertebral artery was entered by chance. The radio-opaque medium spread not only in the area of distribution of the vertebral and basilar arteries but flowed forward through the left posterior communicating artery (arrows) into the carotid syphon and its branches.

This, per se, is a sign of lowered pressure in the internal carotid artery.



Fig. 4.

The same patient as in Figure 3. By puncture of the left common carotid artery the diagnosis of thrombosis in the internal carotid artery has been verified.

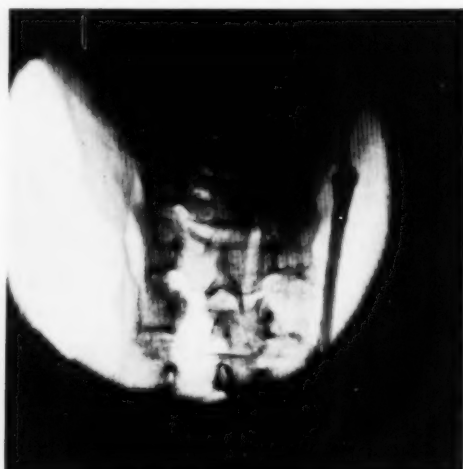


Fig. 5.

If filling of the external carotid artery and its branches only has been observed in the first pictures, it must be ascertained by an exposure such as this (or as in Figure 4) that the tip of the needle is situated in the common carotid artery and not in the external carotid artery.

None of the patients suffered from serious cardiac conditions rendering emboli of cardiac origin probable.

In no less than 3 of the patients the symptoms occurred in direct relation to severe head injuries, a relationship which is also recognized from the clinical observations of intracranial thrombosis and which is of a certain interest in insurance cases.

SIDE INVOLVED

In 14 cases the occlusion of the carotid artery was left-sided, in 12 right-sided, while in one case the condition was bilateral. This difference is naturally of no significance in a material such as this, but it is re-encountered in materials of apoplexy in which a slight but this time significant preponderance of left-sided cranial affection is registrable.

COURSE OF THE DISEASE

Ten of the cases commenced insidiously and progressed steadily or more or less in attacks ("tumour type").

Seventeen cases commenced in apoplectic manner; loss of consciousness occurred, however, in only 4 of the cases. Among these 17 patients brief, complete or practically complete remissions, lasting for hours or days, occurred in 3 cases ("cerebral spasm type").

In 5 cases the condition remained stationary or slow remission occurred ("cerebral apoplexy type").

In 5 cases progression occurring in attacks took place in the subsequent period ("cerebral thrombosis type").

In 3 cases the course of the disease was markedly intermittent ("paralytic attack type").

The duration of those symptoms which could reasonably be attributed to the demonstrated thrombosis of the carotid artery varied from days to years, but in the majority of cases, 1-6 months had elapsed prior to admission for investigation in a neurological department.

In 7 patients the disease had been present for 2 years or more, while in one patient the carotid thrombosis had already been verified arteriographically 5 years previously.

Three patients died during or shortly after the period of hospitalization.

From a material such as this and without systematic follow-up examination, little can be said as regards the prognosis concerning restitution or life except that the course is very unpredictable and that the tendency to recurrence of symptoms is great.

CLINICAL FINDINGS

In the following table, an attempt has been made to register the incidence of the neurological findings in the 27 patients.

Table 1.

Loss of consciousness: 4.
Torpidity and/or severe dementia: 12.
Headache as the dominant symptom: 10.
Deprivation symptoms from primary motor areas: 19. (Positive Babinski's sign in 10 of these only).
Affection of higher integrating motor functions only: 3.
Deprivation symptoms from primary sensory centres: 14.
Affection of higher integrating sensory functions only: 2.
Paraesthesiae: 7.
Motor aphasia: 12 (out of 14 patients with affection of left hemisphere).
Sensory aphasia: 7.
Hemianopic affection of visual field: 6.
Conjugal deviation of the eyes: 3.
Ipsilateral atrophy of optic papilla: 3.
Anisocoria: 3.
Stasis of papilla: 1.
Pronounced extrapyramidal symptoms: 2.
Seizures: 1.

The majority of these symptoms and to a certain extent their distribution are known from the clinical picture of cerebral apoplexy. However, some of the symptoms appear to deviate somewhat, *e.g.*, the frequent incidence of prolonged severe headache not only in hypertensive patients and the not infrequent incidence of paraesthesiae. The ipsilateral papillar atrophy (*i.e.*, contralateral in relation to the symptoms in the extremities) and possible ischaemic retinal changes constitute the classical combination of symptoms which in certain cases render the diagnosis of carotid thrombosis possible prior to arteriography.

The table suggests immediately that very extensive cortical regions are concerned in the disturbance of function with deprivation symptoms from primary efferent and afferent areas, from fields of association, disturbances of visual conduction, reduction of intellect etc., but it is not directly evident from the table that the deprivation symptoms are frequently very "spotted" in their corticotopographical distribution. The authors consider this condition particularly important when compared with the findings in tumours, intracranial thrombosis and haemorrhage.

The authors will not venture to express an opinion as regards the extent to which the striking absence of Babinski's sign in the cases with hemispherically determined pareses has any systematic neurophysiological background and, therefore, any significance in the differential diagnosis or whether it is merely a random finding.

As only a minority of readers obtain a vivid impression of the clinical state of the patients from a tabular review of the symptoms, the authors consider the brief account of isolated case histories appropriate. These case histories cannot be called typical as such cases scarcely exist on account of the diverse clinical manifestations in carotid thrombosis; on the contrary

they serve to illustrate how varied the clinical picture may be.

CASE HISTORIES

"Cerebral Apoplexy Type".

I. Female, aged 40 years. Previously healthy. Periodic addiction to alcohol. Became suddenly unconscious without prodromal symptoms. On waking the patient presented the following clinical symptoms:

Right-sided hemiparesis; right-sided hemianaesthesia; complete expressive and slight impulsive aphasia; right-sided hemianopia.

No abnormalities found on ophthalmoscopy, in cerebrospinal fluid, on ECG and in blood pressure. W.R. negative.

EEG: delta focus in left temporal lobe.

Angiography of left carotid artery: Obstruction at bifurcation, no filling of the siphon or its branches. Clinical course: slow and incomplete recovery.

"Cerebral Tumour Type".

II. Female, aged 57 years. Previously healthy. Headache accompanied by nausea for about one month. While the headache became more intense, paraesthesiae developed in the left arm, and subsequently gradually increasing paresis of the left hand and arm occurred.

The patient became periodically confused and very torpid. Objective examination revealed: torpidity; suggestion of left-sided facial paresis of central type; slight supranuclear paresis of left upper limb; astereognosis in left hand with normal superficial sensibility; slight spasticity in left lower limb without paresis.

Ophthalmoscopy: slight sclerosis of retinal arteries. Blood pressure: 155/75 mm Hg.; B.S.R. 39 mm; W.R. negative.

EEG: severe focal abnormality in right temporal region.

Right-sided arteriography: obstruction $\frac{1}{2}$ cm above the bifurcation; scanty filling of the siphon via the ophthalmic artery; no filling of the branches.

Clinical course: no remission.

"Intracranial Haematoma Type".

III. Male, aged 47 years. Developed sensations of numbness in the fingers of the left hand, slight paresis of the left hand and intermittent paraesthesiae of the left cheek two days after trauma to the head with slight symptoms of concussion.

Objective examination revealed: suggestion of reduction of power in the left hand; exaggerated reflexes in the left upper limb; hypaesthesia corresponding approximately to the left ulnar nerve but slightly more extensive. The neurological findings were otherwise normal. X-ray of cranium: no abnormality. X-ray of cervical spine: slight spondylosis.

Blood pressure: 150/100 mm Hg.; B.S.R. 25 mm; W.R. negative; C.S.F.: 15/3 lymphocytes; 53 mg per cent protein. Ophthalmoscopy: normal. EEG: normal.

Right-sided carotid arteriography: obstruction at bifurcation; siphon filling via ophthalmic artery.

Left-sided carotid arteriography: normal but filling of both anterior cerebral arteries via the anterior communicating artery.

Clinical course: good remission.

"Paralytic Attack Type".

IV. Male, aged 49 years. During the past 3 years the

patient had experienced a total of approximately 50 attacks lasting from half an hour to several days with right-sided hemiparesis and aphasia but without loss of consciousness.

No remission of symptoms occurred following the final attack, and the following signs were found on objective examination:

Right-sided hemiparesis; expressive aphasia; slight central aphasia.

Ophthalmoscopy: normal. Blood pressure: normal; C.S.F.: normal; W.R. negative in blood and C.S.F.; EEG: severe focal abnormality in left temporal region.

Left-sided carotid arteriography: obstruction at bifurcation; no siphon filling.

Vertebral arteriography: good filling of siphon with flow into left middle and anterior cerebral arteries via the posterior communicating arteries.

Clinical course: no remission.

"Pure Pyramidal Tract Type".

V. Male, aged 57 years. Developed monosymptomatic steadily progressive left-sided "peroneal palsy" in the course of 8 days.

Objectively: slight spastic paresis of the left lower limb, most pronounced on dorsiflexion of the foot with exaggeration of the reflexes and left positive Babinski's sign.

Neurological findings otherwise normal.

X-ray of cranium: no abnormality. X-ray of spine: lumbar spondylosis.

C.S.F.: normal; blood pressure: 110/70 mm Hg.; B.S.R.: 4 mm; W.R.: negative; EEG: normal; ophthalmoscopy: normal.

Right-sided carotid arteriography: obstruction at bifurcation; scanty siphon filling via the branches of the external carotid artery with flow into the middle cerebral artery.

Clinical course: some remission.

VI. The patient with pulseless disease and bilateral occlusion of the carotid arteries was a female, aged 52 years. The case report has been published in detail elsewhere (17) and the authors will therefore in the present paper limit themselves to mentioning the facts that the clinical picture in this case was characterized by early severe signs of aging, muscular fatigue also in the chewing muscles, headache occurring in attacks, disturbances of vision partly as flickering scotomata and partly as transient defects of the visual fields and periodic paraesthesiae. The findings on ophthalmoscopy were typical of Takayasu's syndrome.

Vertebral arteriography showed filling of both internal carotid systems.

SPECIAL INVESTIGATIONS

Examination of the Cerebro-Spinal Fluid does not appear to render any information of value in the differential diagnosis in cases of carotid thrombosis. Among the 11 patients in whom lumbar puncture was performed, 6 had entirely normal spinal fluid, 2 had slight hyperalbuminosis and 3 had, in addition, slight pleocytosis.

Electro-Encephalography.

In 20 of the patients, EEG was performed on one or more occasions. In 15 out of the 20, a typical delta focus was found: localized irregular activity with a frequency of 3 c/s or less with

high amplitude. Of these foci, 6 were localized to the temporal region, 5 to the fronto-temporal region, 1 to the frontal region, 2 to the parietal region and 1 to the parieto-occipital region.

It was striking that all these delta foci were characterized by the absence of superimposition by alpha activity, probably indicating that the process extended entirely out to the cortex as clearly illustrated in the cases which came to autopsy.

One patient showed slight dysrhythmia with reduction of amplitude over the entire cerebral hemisphere affected. Another patient showed entirely diffuse dysrhythmia and only 3 patients had completely normal EEG findings. In one case, spikes and paroxysmal dysrhythmia of epileptic type was registered.

The authors consider that these EEG findings are of interest compared with the EEG findings in cerebral apoplexy where delta foci are predominantly encountered in patients suffering from cerebral haemorrhage, while cases of intracranial thrombosis most frequently present normal EEG findings or slight dysrhythmia (7).

Air Encephalography was carried out in 3 of the patients only and in each of these, thrombosis of several years' duration was concerned. In one case, massive ipsilateral atrophy with severe changes resembling porencephaly was found, while in the other two patients the atrophy was less pronounced although definite.

Findings on Arteriography.

All the arteriographies were carried out by percutaneous puncture. Restless or very nervous patients were anaesthetized while in other cases local anaesthesia was employed. Schönander's cassette changer was employed which permits 3 rapid exposures of the lateral photograph and two antero-posterior photographs; seriography was not employed in any case. An attempt was made to photograph the tip of the injection needle in the lateral photographs, but in those cases in which this was unsuccessful, supplementary photographs of the neck were taken during a further injection. The radio-opaque medium employed was approximately 6 ml 35 per cent or, in some cases, 42.5 per cent Diodon or Trijodyl; no complications attributable to the angiography were observed. On the other hand, no clinical improvement attributable to the investigation was noted, contrary to the observation made by Livingston et al.

In one case it was not possible to palpate the carotid artery on the affected side; arteriography was therefore performed on the opposite side and ample filling of the branches of the internal carotid arteries in both hemispheres was obtained.

In another case, palpation of the carotid pulse was impossible on either side; arteriography was then performed in the left vertebral artery, and

via the basilar artery and the posterior communicating arteries ample filling of the carotid branches in both hemispheres was obtained.

In a third case, the first puncture entered the left vertebral artery from which spontaneous filling of the left cerebral branches of the carotid artery occurred. Left carotid arteriography carried out later revealed obstruction of the internal carotid artery at the bifurcation. Obstruction of the internal carotid artery was localized in nearly all cases to the immediate neighbourhood of the bifurcation of the common carotid artery. In an isolated case only, the radio-opaque medium extended 5 cm up into the internal carotid artery.

It has been maintained that interruption of the column of radio-opaque medium cannot be regarded as reliable evidence of the lower limit of the vascular obstruction, as the radio-opaque medium would have difficulty in entering the stagnant column of fluid which might be present in the lower segment of the internal carotid artery caudal to an obstruction (Riishede).

The authors of the present paper do not venture to adopt a definite attitude to this question; they have, however, observed a case of obstruction of the upper segment of the carotid siphon (not spontaneous) in which ample filling of the entire internal carotid artery was seen even at an early phase of the arterial picture. (This case is not included in the present material).

The channels available for the blood supply to the region of distribution of an obstructed internal carotid artery are the following:

I. From the internal carotid of the opposite side via the anterior communicating artery.

II. From the basilar artery to the posterior cerebral artery via the posterior communicating artery.

III. From the external carotid artery, primarily via the ophthalmic artery and possibly via the meningeal arteries.

Examples were given above of the verification by arteriography of the two modes of anastomosis first mentioned; filling of the carotid siphon (with or without branches) via the ophthalmic artery was observed in 13 out of the 27 cases in this material. The evaluation of these anastomoses may be uncertain both radiologically and clinically. Difficulty is encountered in quantitative evaluation of the filling of the siphon, as sufficiently numerous phases in the vascular filling have not been recorded in all cases for the evaluation of the possible filling of the anterior and middle cerebral arteries.

Out of perhaps unnecessary fear of further compromising the function of the already injured cerebral vascular system, the authors refrained from investigating with injections of radio-opaque media in the opposite carotid or the vertebral-basilar arteries.

In this connection the authors quote Webster et al. (21): "What has been identified in the past as the "carotid sinus reflex", involving loss of consciousness upon compression of the carotid bulb, has been observed as a phenomenon present in patients with either a complete or partial carotid occlusion. Brief compression of the unoccluded carotid in some of these patients results in syncope without a change in cardiac rhythm, rate or blood pressure. The electroencephalographic pattern suggests that cerebral ischemia occurs under these circumstances."

Nor have the authors of the present paper felt convinced that such a purely morphological analysis of the anastomoses such as arteriography of the contralateral carotid or vertebral arteries could render information of any significance for the evaluation of the function of the affected hemisphere at a period days, weeks or months after the first or the acute insult.

The anatomical relations will naturally become of interest when the surgical possibilities for thrombectomy mentioned by Søndergård & Riishede (18) become available.

COMPARISON BETWEEN THE ARTERIOGRAPHIC AND CLINICAL FINDINGS

In Table 2 an attempt has been made to compare the findings on arteriography with the most striking clinical deprivation symptoms and with the course of the disease with the object of obtaining information regarding the relative significance of the various systems of anastomosis as demonstrated by arteriography.

Table II.

Comparison between Deprivation Symptoms and Anastomoses of the External Carotid Artery Demonstrable on Arteriography.

No siphon filling.

1. Severe paresis + aphasia
Sensory paresis
Hemianopia
Remission
2. Severe paresis + sensory paresis
Loss of consciousness
Remission
3. Severe paresis + aphasia
No sensory paresis
No remission
4. No paresis
No sensory paresis
Ipsilateral atrophy of papilla
(Vertebral arteriography: filling of carotid system on both sides)
Progression
5. Severe paresis + aphasia
Sensory aphasia
Hemianopia
Loss of consciousness
Remission
6. Slight paresis
Slight sensory paresis
Ipsilateral atrophy of papilla
Progression

7. Severe paresis
Sensory paresis
Loss of consciousness
Hemianopia
(E. E. G., one year later: slight dilatation of ventricles)
Remission
8. Severe paresis + aphasia
Sensory paresis
Hemianopia
Loss of consciousness
Ipsilateral ischaemic retinal changes
(Arteriography of opposite carotid: bilateral filling of anterior cerebral arteries; no siphon filling). E. E. G., 4 years later: enlarged left ventricular system + porencephaly
Remission
9. Severe paresis + sensory paresis
Conjugal deviation of the eyes
Remission
(E. E. G., 5 years later showed greatly enlarged right ventricular system + massive porencephaly)
10. Slight paresis
Slight sensory paresis
(Arteriography of contralateral carotid: bilateral filling of anterior cerebral arteries + siphon filling and filling of middle cerebral arteries)
Progression
11. Severe paresis + aphasia
Sensory paresis
Hemianopia
No remission
12. Slight paresis + aphasia
No sensory paresis
(Filling of entire carotid system from vertebral artery)
Remission

Siphon filling via external carotid but no flow into main branches.

13. Severe paresis + conjugal deviation of the eyes
Sensory paresis
Torpidity
Progression
14. Slight paresis + aphasia
No sensory paresis
Remission
15. Sensory paresis
No motor paresis
(Bilateral filling of anterior cerebral artery from contralateral carotid; no siphon filling)
Remission
16. Slight paresis
No sensory paresis
No remission

As above + flow into middle cerebral artery.

17. Severe paresis + aphasia
Sensory paresis
No remission
18. Severe paresis + sensory paresis
Remission
19. Slight paresis
No sensory paresis
Remission

As above + flow into anterior cerebral artery (but not into middle cerebral artery).

20. Severe paresis + aphasia
Sensory paresis
No remission
21. No paresis. Aphasia
No sensory paresis
No remission

Siphon filling via external cerebral artery + flow into middle and anterior cerebral arteries.

22. Slight paresis + aphasia
No sensory paresis
Progression
23. No paresis
No sensory paresis
Remission
24. Severe paresis +
conjugal deviation of the eyes
No sensory paresis
Progression
25. Slight paresis
No sensory paresis
Remission
26. No paresis. Slight aphasia
Sensory paresis
Progression
27. Slight paresis
Hemianopia
No sensory paresis
Torpidity
Remission

No particular relation can be anticipated between the demonstrable filling of the anastomosis and the clinical findings, as arteriography per se will not necessarily render any information concerning the anastomotic conditions unless performed in the critical period immediately after the vascular catastrophe.

The findings are thus ambiguous, but it should be noted that the two cases in which apparently satisfactory filling of the entire internal carotid system on vertebral arteriography was obtained are among the mildest in the material. This also holds true for the cases in which the entire affected internal carotid system was found to fill adequately from the opposite internal carotid artery via the anterior communicating artery, while one of the two cases in which carotid arteriography on the opposite side rendered filling of the anterior cerebral artery on the affected side only belongs to the most severe cases.

The significance of the anastomotic filling via the ipsilateral ophthalmic artery from the external carotid artery is demonstrated by the observation that among the 15 cases in which siphon filling could be demonstrated via this route, no loss of consciousness had occurred and only 5 of the patients had severe paresis, while 4 cases with loss of consciousness and 8 with severe paresis occurred among the 12 where no siphon filling was obtained via the ophthalmic artery. The 6 cases in which, in addition to siphon filling via the ophthalmic artery, flow into both the middle and anterior cerebral arteries was observed belong, with one exception, also to the very slightest.

On the other hand, Table 2 does not demonstrate any relation between the prognosis as regards restitution and demonstrable siphon filling via the ophthalmic artery.

If any conclusion is to be drawn from Table 2, it must be that the anastomoses from the area of the basilar artery via the posterior communicat-

ing arteries and from the contralateral internal carotid artery are the most important in reducing the sequelae of occlusion in the circulation of the internal carotid, but that anastomoses via the ipsilateral ophthalmic artery also play a certain rôle in this connection.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The clinical diagnosis of thrombosis of the internal carotid artery is difficult and if arteriography is not resorted to, it can only be established in the rare cases in which contralateral hemispherical symptoms occur simultaneously with ipsilateral eye symptoms (atrophy of the papilla, ischaemia, retinal changes, cataract, atrophy of the iris, etc., and this is only observed when the thrombosis also affects the common carotid or the external carotid arteries.

The diagnosis must be borne in mind in all cases of intermittent or progressive unilateral hemispherical deprivation symptoms, whether these occur in an apoplectic manner or not, and in rapidly developing cryptogenic conditions of dementia. Suspicion must particularly be directed towards the cases in which the deprivation symptoms assume a more spotted cortical character.

On account of the frequent complaint of headache in patients suffering from carotid thrombosis, cerebral tumour appears to present a greater difficulty in the differential diagnosis than does cerebral apoplexy. It should be noted that among 17 out of the 27 cases in the present material, cerebral tumour was regarded as the most probable diagnosis prior to arteriography.

Palpation of the carotid arteries in the neck is a diagnostic aid of doubtful value unless the common carotid artery is involved. In only 3 of the patients in the present material could definitely reduced pulsation on the affected side be demonstrated on palpation.

Electroencephalography may apparently become a diagnostic aid of value as no less than 75 per cent of the patients in this series on whom electroencephalography was performed showed marked delta foci without tumour potentials, and in cases of apoplexy this is only found in cases of extensive haemorrhage which can often be excluded because of blood-stained cerebro-spinal fluid.

Examination of the cerebro-spinal fluid does not otherwise render any information of value in the differential diagnosis of cases of thrombosis of the internal carotid artery.

It should, however, constantly be borne in mind that an apoplectic commencement of the disease suggests a vascular catastrophe while an epileptiform commencement suggests tumour.

The only certain diagnostic aid is arteriography of the carotid artery, and the present material must be regarded as evidence in favour of more extensive employment of this examina-

tion, not only in view of tumour but also when cerebral thrombosis or haemorrhage are suspected.

References:

- 1) Ask-Upmark, E.: Nord. Med. 1955, 54: 1237.
- 2) Chiari, H.: Verhandl. deutsch. path. Gesellsch. 1905, 9: 326.
- 3) Dalsgård-Nielsen, T.: Acta Psychiat. Neurol. Scand. 1955, 30: 169.
- 4) Decker Von, K. & E. Holzer: Fortschritte auf dem Gebiete der Röntgenstrahlen 1954, 80: 565.
- 5) Fisher, M.: Arch. Neurol. Psychiat. 1954, 72: 187.
- 6) Fisher, M.: Arch. Neurol. Psychiat. 1951, 65: 346.
- 7) Harvald, B. og E. Skinhøj. Nord. Med. 1956, 55: 679.
- 8) Hultquist, G. T.: Über Thrombose und Embolie der Arteria Carotis. Stockholm 1942. Gustav Fischer, Jena.
- 9) Johnson, H. C. & A. E. Walker: J. Neurosurg. 1951, 8: 631.
- 10) Knudsen, Verner: Ugeskr. Læger 1956, 41: 1187.
- 11) Kragebühl, H. & G. Weber: Helvet. Med. Acta 1944, 11: 289.
- 12) Livingston, K. E., A. Escobar & G. D. Nichols: J. Neurosurg. 1955, 12: 336.
- 13) Murphy, J. P.: Cerebrovascular Disease. The Year Book Publishers, Chicago 1954.
- 14) Olivarius, B. de Fine & Jørgen Therkelsen: Ugeskr. Læger 1956, 41: 1193.
- 15) Pailles, J. & L. Christophe: Les Thromboses, de la carotide interne et de ses branches. Masson et Cie Editeurs, Paris 1955.
- 16) Potter, J. M. & F. M. Taylor: Arch. Neurol. Psychiat. 1955, 74: 414.
- 17) Rasch, P. J. & H. H. Jacobsen: Nord. Med. 1956, 56: 1328.
- 18) Søndergård, T. & J. Riishede: Restoration of Carotid Circulation in Carotid Thrombosis. Scandinavian. Neurosurg. Soc. 12th Congress 1956.
- 19) Torkildsen, A. & K. Koppang: J. Neurosurg. 1951, 8: 269.
- 20) Voris, H. C.: J. Neurosurg. 1951, 8: 119.
- 21) Webster, J. E., E. G. Gurdjian & F. A. Martin. Neurology 1956, 6: 491.

SERUM GLUTAMIC OXALACETIC TRANSAMINASE IN MYOCARDIAL INFARCTION

ITS DIAGNOSTIC AND PROGNOSTIC VALUE

By P. FROM HANSEN and THOMAS LAURSEN

As reported for the first time by LaDue, Wroblewski & Karmen (1954), serum glutamic oxalacetic transaminase activity (SGO-T) is of help in diagnosing myocardial infarction and other conditions with tissue necrosis or necrobiosis. The aim of the present investigation is to throw light on the value of SGO-T in the diagnosis of myocardial infarction, as compared with the clinical judgement and electrocardiography, and also to examine whether any relationship exists between the SGO-T values found and the early mortality.

METHOD

The determination of SGO-T is relatively simple. The addition of serum to a medium consisting of L-aspartic acid and α -ketoglutaric acid converts this partly to glutamic acid and oxalacetic acid. The amount of oxalacetic acid formed during a definite time interval is a measure of the enzyme activity. This can be

determined directly (Karmen, Wroblewski & LaDue, 1955) or indirectly by converting the oxalacetic acid to pyruvic acid by boiling (Henley & Pollard, 1955), the pyruvic acid being determined enzymatically with the aid of lactic acid dehydrogenase and reduced diphosphopyridine nucleotide (DPNH⁺). The method of Henley & Pollard, which has been used in the present material, has the advantage that the transamination process takes place at a constant and reproducible temperature.

The enzyme activity is expressed as the number of micromols of oxalacetate formed under the given experimental conditions, calculated per hour per milliliter of serum. In our use of the method, the standard deviation of the analysis is calculated from the double analyses in an arbitrarily chosen month. For values under 5.0 the standard deviation of the analysis is 0.1, and for values between 5.0 and 15.0 it is 0.2.

Henley & Pollard found, in a material of 44 normal persons, a mean value of 1.34 units with a biological standard deviation of 0.12. In a normal material consisting of 70 donors we have found a mean value of 0.9 with a biological standard deviation of 0.3.

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This work has been aided by a grant from Arvid Nilsson's Foundation.

We have chosen 1.7 units as the upper limit of the normal range.

MATERIAL

The patient material comprises 147 persons admitted to various medical departments in Copenhagen*). The diagnosis on admission was unquestionable or suspected recent myocardial infarction.

In about half the patients, SGO-T was determined immediately after admission, approximately 6 hours after, approximately 18 hours after, 3 days after and 7 days after admission. In the remaining patients, the enzyme activity was determined at more varying times. Two or more determinations were made in all cases.

Each patient was characterized by the maximum value found. These maximum values were divided into four groups, comprising normal values (38 in all), values from 1.7 to 4.9 (49), from 5 to 9.9 (30) and values of 10.0 or above (30). In the following, an account will be given of the clinical evaluation for each of these groups, together with the electrocardiographic changes.

In order to judge the prognostic value of the SGO-T determination, it is related to the mortality during hospitalization and compared with the relation of fever, white cell count and erythrocyte sedimentation rate to the mortality.

RESULTS

SGO-T compared with the clinical evaluation.

In 32 cases, the diagnosis of no myocardial infarction was made in the course of the hospitalization, in 26 cases the diagnosis was uncertain and in 89 patients myocardial infarction was judged to be present (Table 1).

Table 1.
SGO-T compared with the clinical evaluation of 147 patients hospitalized for myocardial infarction.

	Clinically no infarction (32)	Clinically uncertain (26)	Clinically certain infarction (89)
Normal SGO-T ...	21	12	5 (-2, see text)
< 5 units	9	13	27
5-10 units	1		29
≥ 10 units	1	1	28
SGO-T raised in ..	34%	56%	94%

Eleven of the 32 patients first mentioned had raised values. One of these patients had heart failure with congestion of the liver, as a possible cause of the rise. No extra-cardial cause of the raised transaminase value could be demonstrated

*) Our thanks are due to the medical departments of Copenhagen County Hospital, Bispebjerg Hospital, Old People's Town, Blegdams Hospital and the Blegdam Epidemic Hospital.

in the remaining 10 patients. Three of these died, and on autopsy two of them showed recent infarcts, with a somewhat older infarct in the third, but no obviously recent one.

The group with clinically uncertain myocardial infarcts comprised 26 cases. SGO-T was found raised in 14 of them. In two of these, a possible extra-cardial cause of the rise could be considered. The one patient had congestion of the liver, the thymol turbidity test being abnormally high, while in addition the course of the SGO-T deviated from the usual with myocardial infarction, the values remaining moderately raised for more than one week. The other patient developed an attack of gout. No extra-cardial cause of the raised value could be demonstrated in the remaining 12 patients. One of these died, and autopsy showed recent scattered necroses in the myocardium.

If the diagnosis of myocardial infarction in this group were based on the rise in SGO-T, it would thus be possible to extract 22 cases of infarction from the 58 clinically uncertain or negative cases, and this diagnosis was autoptically confirmed in three of the four patients who died. Among these 58 cases, 33 had normal SGO-T: one died and autopsy showed no recent infarction.

Among the 89 clinically certain cases of myocardial infarction, SGO-T was found raised in 84 cases. Five patients had normal values; in two of these the test was made more than a week after the onset of the precordial pain, so that the possibility of these patients having had raised values cannot be excluded. The other three cases were all of a very mild nature, with slight pain and subfebrile temperature, the electrocardiogram showing slight transient changes in S-T and T.

Twenty-three of the remaining 84 with raised SGO-T died; twenty-one of them had autopsy carried out, and all showed recent infarctions.

SGO-T compared with the electrocardiographic changes.

It will be seen from Table 2 that SGO-T in patients with normal electrocardiograms was raised in 43 per cent of the cases. Approximately the same distribution was found both in the

Table 2.
SGO-T compared with the electrocardiographic changes in 147 patients hospitalized for myocardial infarction.

	Normal ECG	Branchblock etc.	Constant pathological changes in T	Transient changes in S-T or T	Transmural infarction
Normal SGO-T ...	8	6	14	10	
< 5 units	4	4	7	17	17
5-10 units	1	1	1	9	18
≥ 10 units	1			3	26
SGO-T raised in ..	43%	46%	36%	74%	100%

patients who had constant pathological changes of the T waves and in those who had other signs which were not certain indications of infarction, including 5 cases of bundle-branch block, three of which had raised SGO-T. On the other hand, patients with transient changes in the ST-segment or T-waves showed raised values in 74 per cent of the cases, and excessively high values (≥ 10 units) in 5 per cent of the cases. With typical anterior or posterior wall changes in the limb leads, a rise was found in 100 per cent, and an excessive rise in 44 per cent.

SGO-T in other diseases than myocardial infarction.

SGO-T has been investigated in some diseases which can cause difficulties in the differential diagnosis from myocardial infarction.

Two patients with acute cholecystitis had raised values (maximum 3.4 and 15.4 units): in the latter patient the SGO-T course was similar to that in myocardial infarction, with a quick rise and fall.

Six patients with pulmonary infarction and one patient with thrombosis of the pulmonary artery all had normal values. The same was the case with 7 patients with angina pectoris. Of 5 patients with heart failure and enlarged liver, one had a slightly raised SGO-T, the rest had normal values.

The time of measurement of maximum SGO-T values.

This is of practical value for the diagnosis of myocardial infarction. Determinations from the 1st, 2nd and 3rd days after the onset of the precordial pain are available for 31 patients with clinically certain infarction and with raised SGO-T. In 24 patients the maximum was found on the 2nd day, in 4 on the 1st day and in 3 on the 3rd day, or later. Two of the last mentioned 3 patients had repeated attacks of pain, some of those presumably pre-occlusion pain.

The prognostic value of SGO-T.

Among the 89 patients with certain myocardial infarction, the mortality during the hospitalization was correlated with the magnitude of SGO-T. Table 3 shows increasing mortality with increasing SGO-T value.

Table 3.

SGO-T compared with the mortality during hospitalization of 89 patients with clinically certain infarction.

Normal SGO-T ...	0 died out of 5	
< 5 units	3 " " " 27	= 11%
5-10 units	5 " " " 18	= 28%
≥ 10 units	13 " " " 27	= 50%

To throw light on the prognostic value of SGO-T in relation to the criteria hitherto used, the degree of fever, white cell count and erythrocyte sedi-

mentation rate have also been compared with the mortality during hospitalization.

This comparison was made in 65 patients with clinically certain myocardial infarction, and on whom all the four examinations mentioned above were carried out. The boundary between high and low values in each of these tests has been so chosen that the patient groups so obtained were approximately equal in size.

Table 4.

Comparison between mortality during hospitalization and SGO-T, body temperature, leucocyte and sedimentation rate, for 65 patients with clinically certain infarction, who had all four values measured.

SGO-T < 6 units	3 died out of 32	= 9%
SGO-T ≥ 6 units	13 " " " 33	= 39%
Temperature < 38.5° C 4	" " " 32	= 13%
Temperature $\geq 38.5^\circ$ C 12	" " " 33	= 36%
Leucocyte count < 10,000 1	" " " 26	= 4%
Leucocyte count $\geq 10,000$ 15	" " " 39	= 38%
SR < 50 mm/hr.	6 " " " 29	= 21%
SR ≥ 50 mm/hr.	10 " " " 36	= 28%

The result appears from Table 4, which shows that SGO-T provides approximately the same figure in evaluating the early mortality as do temperature and leucocytosis, but more than is the case with the sedimentation rate.

DISCUSSION AND CONCLUSION

A raised SGO-T is almost inevitably found in clinically and electrocardiographically certain cases of myocardial infarction, which fact agrees with the findings of previous authors (1, 2, 4, 6, 8, 10). The diagnostic advantage in the use of the SGO-T determination in such cases — mainly the transmural infarctions — lies in the possibility of early diagnosis, the SGO-T rising 2-4 hours after the occlusion, at which time the electrocardiogram has still not always shown certain transmural signs. It is also possible by means of the SGO-T determination to decide whether the pain is a premonitory pre-occlusion pain without infarction, or due to the infarct itself. Finally, by following the patient's SGO-T during the course of the disease, new infarctions can be recognized, which would otherwise be clinically masked by the initial infarct.

In clinically doubtful cases of infarction, we have found raised values in $\frac{1}{3}$ to $\frac{1}{2}$ of the cases. LaDue & Wroblewski's material gave the somewhat lower frequency of 10 in 60 slightly raised, but Ostrow et al. found a considerably higher frequency: 21 in 26. Iversen et al. likewise found a high frequency: 19 raised in 21. It is generally agreed that the SGO-T determination within the group of clinically and electrocardiographically doubtful cases is of considerable discriminatory diagnostic value. The same is the case for that group of patients suspected of having myocardial infarction, but where the diagnosis has been dropped for clinical reasons,

and where the electrocardiogram has either been normal or has been difficult to interpret on account of previous changes.

Without a precise clinical evaluation of the case, however, false positive values of SGO-T can arise. Acute pancreatitis (1) and pulmonary infarctions later in the course of the disease (9) can thus give raised values. Acute cholecystitis must also be stressed as a source of error, as the course of the SGO-T is quite similar to that typical for myocardial infarction. Prognostically, the height of the SGO-T value gives a guide to the early lethality: the figures found for this in our material correspond well to those given by Chinsky et al., but for this purpose seem no better suited than the objective criteria hitherto used, such as high fever and leucocytosis, when it is a case of clinically certain — mainly transmural — infarction.

SUMMARY

One hundred and forty-seven patients hospitalized with presumed or certain recent myocardial infarction were followed with serum glutamic oxalacetic transaminase determination. Raised values were found in 97 per cent of the clinically certain cases and in one half of the clinically uncertain cases, as well as in one third of those cases where it was considered that myocardial infarction could be clinically excluded.

Correlated with the electrocardiogram, there

was 100 per cent agreement with the signs of transmural infarction, raised SGO-T in $\frac{3}{4}$ of the cases with variable deviations in ST or T, and in $\frac{1}{3}$ to $\frac{1}{2}$ of the remaining electrocardiograms, including the normal ones.

The early mortality showed good correlation with the height of SGO-T, but it does not appear that the prognosis in clinically certain cases is better evaluated by this test alone than by the known tests such as height of fever and leucocytosis.

References:

- 1) Baron, D. N., J. Bell & C. Oakley: *Lancet* 1956, II: 897.
- 2) Chinsky, M., G. L. Shmagranoff & Sol Sherry: *J. Lab. Clin. Med.* 1956, 47: 108.
- 3) Henley, K. S. & M. H. Pollard: *J. Lab. Clin. Med.* 1955, 46: 785.
- 4) Iversen, K., N. U. Bang & S. Madsen: *Ugeskr. Læger* 1957, 119: 239.
- 5) Karmen, A., F. Wroblewski & J. S. LaDue: *J. Clin. Invest.* 1955, 34: 126.
- 6) Kallus, A. A. jr., C. Samenson & R. Watanabe: *Circulation* 1955, 12 (4): 729.
- 7) LaDue, J. S., F. Wroblewski & A. Karmen: *Science* 1954, 120: 497.
- 8) LaDue, J. S. & F. Wroblewski: *Circulation* 1955, 11: 871.
- 9) Ostrow, B. H., D. Steinberg, H. E. Ticktin, G. N. Polis & J. M. Evans: *Circulation* 1956, 14: 790.
- 10) Shabetai, R., A. Iglauer & D. M. Anderson: *Brit. M. J.* 1957, March 9, 555.

CARDIAC FUNCTION IN FUNNEL CHEST

TWENTY-SIX PATIENTS INVESTIGATED BY CARDIAC CATHETERIZATION

By J. FABRICIUS, H. GÖSTA DAVIDSEN and A. TYBJERG HANSEN

The material consists of 26 patients with funnel chest. Of these, 22 had funnel chest at the sole abnormality while 4 had complicating heart disease (2 cases of ventricular septal defect, 1 case of patent ductus arteriosus and 1 case of anomaly of the aorta). The material comprises 16 males and 10 females. As appears from the Table, the ages of the patients varied from 7 to 62 years, the average age being 21 years.

In a survey by Wachtel et al. the various theories concerning the pathogenesis are reviewed. Funnel chest is, as a rule, discovered at birth but becomes more pronounced in the course of

years. The patients gradually develop an asthenic appearance, the volume of the thorax diminishes and the heart is displaced to the left.

RADIOLOGICAL EXAMINATION

Funnel chest may present various degrees of severity and may assume various forms (Evans). In our material, subdivision into degrees of severity of the funnel chest was based upon determination of the distance from the back of the sternum to the anterior surface of the vertebral column, as measured on X-ray photographs in the lateral projection, exposed at a film-focus distance of 1.5 metres. Roesler states that the normal distance is 10.3 cm in men and 9.2 cm in women when measured orthodiagraphically. In funnel chest, the distance may be zero (Brodkin). In our material, the minimum distance from the

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sternum to the vertebral column was 1 cm. Distances less than 5 cm indicate severe cases, from 5—7 cm moderate cases and over 7 cm slight cases.

Out of the author's 22 patients with uncomplicated funnel chest, 10 were severe, 4 moderate and 8 slight according to this subdivision. In the Table, the patients are registered according to the sterno-vertebral distance.

In the moderate and severe cases, typical changes are demonstrable on X-ray examination (Evans; Master et al. and Albrechtsen). The heart is displaced to the left so that the right border of the heart may cover the vertebral column, rendering measurement of the transverse diameter of the heart difficult. The left border of the heart is straightened and the pulmonary conus prominates, and the heart assumes the appearance which is normally seen in the right oblique diameter. The frontal area of the heart may become enlarged (Myhre) while in the lateral position it appears flattened (*cor planum*). As the heart is displaced to the left, the right hilus is seen more distinctly than normally and this may be erroneously interpreted as pulmonary disease (Albrechtsen). In the 22 patients in the present material, the heart was increased in the transverse diameter in 7, displaced in 13 while in 11 the conus was prominent. The displacement of the heart to the left may be recognized clinically by the presence of the apex beat more laterally than normal.

In 3 patients angiocardiology was performed. This demonstrated the displacement of the heart to the left, that the heart was compressed antero-posteriorly and lay close to the thoracic wall. Two patients were placed lying on the left side without this causing demonstrable reduction of the circulation in the right lung.

MURMURS

In patients suffering from funnel chest, a systolic murmur is frequently heard, which may lead to the assumption that a cardiac lesion is present. Master et al. found murmurs in 15 out of 25 patients with funnel chest; Myhre in 11 out of 21; Wachtel et al. in 7 out of 13 and Ernberg in 22 out of 32. In the present material, 17 out of 22 had a systolic murmur of weak to moderate intensity (grade 1—3). There was no interdependence between the loudness of the murmur and the degree of funnel chest. In most cases the murmur was loudest along the left border of the sternum, but it might be most pronounced at the apex or in the pulmonary area. The murmur was most frequently short and soft and was heard over a relatively small area. Evans stated that the murmur was most marked in the funnel and, consequently, most probably due to the impact of the heart against the chest wall. The murmur may disappear after operation (Lindskog et al., Wachtel et al.).

The second heart sound over the pulmonary artery is frequently accentuated and Ernberg found an accentuated P_2 in 6 out of 32 patients with funnel chest. In the present material, accentuated P_2 was found in 7 out of 22 patients with an average age of 19.7 years.

Reduplicated P_2 was found in 4 patients with an average of 18.5 years. No relationship between the condition of P_2 and the degree of severity of the funnel chest was observed. The authors of the present paper encountered no diastolic murmurs in any case of uncomplicated funnel chest; one patient had funnel chest and patent ductus arteriosus with typical continuous murmur. Following surgical closure of the ductus, the murmur ceased. Ernberg mentions 2 cases with diastolic murmur at the apex and 2 cases with presystolic murmur among 32 patients with funnel chest.

If, therefore, a diastolic murmur is heard in a case of funnel chest, it may be presumed that a complicating cardiac lesion is present. Funnel chest complicated by congenital cardiac disease has been recorded by Edling.

ELECTROCARDIOGRAM

In funnel chest, the electrocardiogram frequently shows right-sided axis deviation (Dressler et al.). In the present material, 10 out of the 22 patients showed normal electrocardiograms while 8 had right-sided axis deviation; of these latter, 7 were over 11 years and the oldest 34 years with rather severe funnel chest (No. 4). Two patients (No.'s 1 and 19) had incomplete and one (No. 12) complete right-sided bundle branch block. One of these patients (No. 19) had pronounced deformity of the thorax and was one of the patients in whom the findings on cardiac catheterization were abnormal. The two other patients had moderately pronounced funnel chest. Only one patient (No. 20) showed left-sided axis deviation.

Master & Stone have described high and pointed P waves in leads II and III in funnel chest. In the present material, a total of 6 patients had abnormal P waves: 4 patients showing abnormally high P waves in lead II (higher than 2.5 mm), one a notched P wave and one a broad P wave (broader than 0.11 sec.). These 6 patients had normal pressures in the right side of the heart so that the abnormal P waves cannot be attributed to high pressure in the atria. The changes in the P waves are independent of the degree of funnel chest and are probably due to rotation of the heart, whereby the localization of the atria in relation to the conducting parts of the thorax (muscles and vessels) deviated from normal. On cardiac catheterization, 3 patients showed increased pressure in the right atrium. These 3 patients had normal P waves.

Precordial leads were recorded in 14 out of the 22 patients. 10 showed normal position of

the transitional zone while 4 showed clockwise rotation. Myhre did not find any abnormal rotation of the heart in 21 patients with funnel chest. Dressler et al. and Wachtel found frequently negative T waves in the precordial leads and are of the opinion that this is due to rotation of the heart. In the present material, no changes in the T waves were found. Wachtel et al. stated further that the QRS complex in V_1 frequently takes the form of rSr' or rSR' and consider this to be a normal variant. In the material, 2 patients showed rSr' and 1 an rSR' complex in V_1 .

PULMONARY FUNCTION

The pulmonary function may be reduced in funnel chest. Thus Master & Stone, Brodtkin and Ravitch stated that the vital capacity may be reduced although it is most frequently normal. Myhre found practically normal figures in 21 patients.

In the present material, the vital capacity was measured in 14 patients and was found to be slightly reduced in 4. Myhre found the maximal breathing capacity somewhat lower than normal and this corresponds to the values found in the present material.

CARDIAC CATHETERIZATION

Catheterization has previously only been performed in a small number of patients. Ravitch catheterized 4 patients and found normal conditions in 2. The third patient showed normal pressures but the recording from the right ventricle was similar to the curve found in cases of constrictive pericarditis, presenting a diastolic dip and an elevated diastolic plateau. The fourth patient had atrial fibrillation with increased pressure in the right ventricle (55/2 mm Hg) and the right atrium (15/8 mm Hg). The circulation time was reduced and the cardiac output was measured as 1.4 litre/min./ m^2 . When the funnel chest had been corrected by operation, the atrial fibrillation disappeared and the pressures and the circulation time became normal.

Lindskog & Felton found abnormal conditions in 1 out of 4 catheterized patients. This patient had increased pressure in the right atrium (22 mm Hg) and reduced cardiac output. Following digitalization, the right atrial pressure fell to 6.5 mm Hg and the cardiac output rose to normal levels.

Myhre catheterized one patient with severe funnel chest. Normal but low pressures were found at rest and after exercise. The cardiac output was normal at rest and was not measured after exercise.

Wachtel, Ravitch & Grishman catheterized 2 patients. In one, normal conditions were present while in the other slight increase of pressure in the pulmonary artery and a fall in cardiac output was found after exercise. The

authors concluded from these findings that the marked restrictions of the intrathoracic space in the cardiac region might not permit an increase of cardiac volume during exercise. This would restrict the diastolic filling of the chambers, and provide a condition which resembles constrictive pericarditis.

The findings on cardiac catheterization of the patients in the present material appear from the Table. Measurements of pressure were undertaken in all patients at rest, but after exercise in 2 patients only. The cardiac output was measured in 6 patients.

In the 22 uncomplicated cases, abnormal pressure conditions were found in 3 (Nos. 9, 18, 19). All 3 had slightly increased pressure in the right atrium; in 1 patient (No. 9) there was, in addition, slightly increased pressure in the right ventricle (33/0 mm Hg) and a slight pressure gradient over the pulmonary ostium. Another patient (No. 19) showed an abnormal ventricular curve with a diastolic dip and elevated diastolic plateau as described in constrictive pericarditis (Tybjaerg Hansen et al.). In addition to the funnel chest, this patient had a severely deformed thorax. A ventricular curve of this nature is very suggestive of an impeded diastole resulting in poor filling of the ventricle and increased pressure in the right atrium.

From the Table it will be observed that the pressures in the pulmonary circulation are relatively low. Pressure measurements were performed with the patients in the horizontal position with a zero level corresponding to the mid-axillary line. The reduced anteroposterior diameter of the thorax possibly causes the zero level to be placed too high in relation to the heart, which renders too low values.

An accentuated pulmonary second heart sound in funnel chest cannot be explained by increased pressure in the pulmonary circulation but must be due to the abnormal position of the heart or the limited distance from the heart to the anterior thoracic wall.

In the 6 patients in whom the cardiac output was measured normal values were found in 5. In one patient (No. 16), who had rather severe funnel chest, the cardiac output was reduced at rest but normal after exercise. This patient had previously undergone an unsuccessful operation for correction of funnel chest. In the 4 patients in whom the cardiac output was measured after exercise, this rose normally.

The 22 patients with uncomplicated funnel chest were supplemented with 4 patients who had, in addition, congenital heart disease. These patients differed clinically from the other patients in the character of the murmur. The patient with patent ductus arteriosus had a typical continuous murmur while the other 3 had marked systolic murmurs. One patient had left axis deviation in the electrocardiogram and one had left-sided

No.	Case no.	Sex	Age	Sterno- Vertebral Dist. cm.	Symptoms	Heart Catheterization Pressures in mm Hg.		Right ventr.	Right atr.	Arterio- Venous O ₂ Diff. in vol. %	Cardiac Output ltr./min./m ²		Vital Capacity.
						PCV	Pulm. art				Rest	Exercise	
1	769	m	32	10	+	11	19/8	19/0	3.5	4.2	4.4	—	low
2	1114	m	18	9	+	9	24/11	24/5	3	2.7	—	—	—
3	1314	m	20	8	÷	9	16/8	16/3	3	3.6	4.5	9.4	normal
4	1421	m	34	8	÷	3	14/2	18/0	1	5.0	—	—	—
5	508	m	25	8	+	7.5	24/9	24/0	1	4.1	—	—	—
6	3394	f	16	8	+	3.5	23/7	23/0	2	4.5	—	—	—
7	3784	m	7	8	÷	11	25/13	25/3	4	—	—	—	—
8	3454	m	15	7.5	÷	3	25/9	30/0	0	3.0	—	—	normal
9	3652	f	12	7	+	11	25/9	33/0	6.5	3.5	—	—	low
10	3358	f	17	6	+	5	18/5	18/0	2	5.2	—	—	normal
11	3158	m	33	5.5	+	7	16/8	20/0	5	4.3	—	—	low
12	1389	m	25	5	÷	3	17/5	17/0	0	4.5	—	—	normal
13	3502	m	15	4.5	+	7	25/12	25/0	2	2.4	7.1	9.1	normal
14	3522	f	11	4.5	+	6	21/9	21/0	1	2.8	—	—	—
15	3340	m	15	4	+	3	12/5	19/0	2	4.1	—	—	low
16	1247	f	21	4	÷	7	18/7	18/0	÷1	3.5	1.8	4.3	normal
17	900	f	20	4	÷	7	23/8	23/0	÷2	1.2	—	—	low
18	3777	m	7	3	÷	10	20/10	24/5	6	5.5	2.9	—	normal
19	3324	f	23	3	+	10	28/11	28/0	8.5	4.7	—	—	—
20	948	m	19	2	÷	3	13/5	13/0	0	4.5	—	—	—
21	964	f	15	2	+	—	16/12	16/0	0	4.6	—	—	—
22	1424	m	14	1	÷	7	21/7	21/0	0	3.7	3.8	6.9	normal
23	3636	f	31	8.5	+	18	30/13	30/0	5	1.2	—	—	ventricular septal defect.
24	990	f	62	7	+	11	23/9	23/0	0	3.2	—	—	aortic stenosis.
25	1172	m	20	6.5	÷	15	25/15	25/0	3	—	—	—	patent ductus arteriosus.
26	1111	m	18	6	+	3	14/7	14/÷1	÷1	4.4	—	—	ventricular septal defect.

bundle branch block. Three of the patients showed a shunt to the pulmonary circulation on cardiac catheterization. Patients who suffer from funnel chest and in whom atypical murmurs, pathological electrocardiographic or radiographic findings are demonstrated should be catheterized on account of the likelihood of additional congenital heart disease.

SYMPTOMS

Symptoms such as exertional dyspnoea, sensation of pressure in the precordium and palpitations occur frequently in funnel chest. Only 8 out of the 22 patients in the present material were symptom-free but the symptoms were independent of the degree of severity of the funnel chest. Several of the patients in this material with severe funnel chest had no symptoms, among these one of the patients (No. 18) with increased pressure in the right atrium. Other patients with slight funnel chest had slight or moderate symptoms.

CONCLUSION

The majority of patients with funnel chest show normal pressure in the pulmonary circulation; only isolated patients with severe funnel chest had increased pressure in the right atrium and a type of pressure curve from the right ventricle resembling that seen in chronic constrictive pericarditis. The displacement of the heart associated with funnel chest may, in severe cases, com-

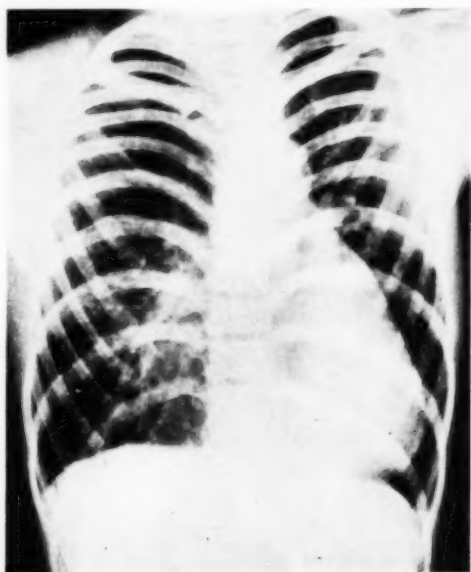
promise the function of the heart by impeding diastole. Reduced cardiac output may be seen. The volume of the lungs may be slightly reduced but this does not result in cardiac complications, particularly not cor pulmonale.

The subjective symptoms may be explained by the reduced thoracic volume and the displacement of the heart, as operative correction of the funnel chest may relieve the symptoms and normalize the pressures (Lester; Ravitch; Therkelsen). Operation in cases of funnel chest is seldom indicated apart from purely cosmetic reasons.

SUMMARY

26 patients suffering from funnel chest, of whom 22 were uncomplicated and 4 complicated by heart disease, were investigated by means of cardiac catheterization. Only 3 out of the 22 showed abnormal conditions of pressure with slightly increased pressure in the right atrium; in one of these, a ventricular curve was found, similar to that in constrictive pericarditis. One out of 6 had reduced cardiac output at rest. The vital capacity may be reduced and the electrocardiogram frequently shows right-sided axis deviation. The symptoms are independent of the degree of funnel chest and the findings on cardiac catheterization. For this reason the indication for surgical treatment appears to be purely cosmetic except in extreme cases.

References: page 257.



Figs. 1 a and b.

X-ray photograph of patient No. 22 showing the heart displaced to the left and the right border of the heart obscured by the vertebral column. Distance between the vertebral column and the sternum 1 cm.

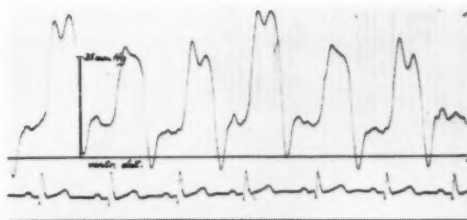
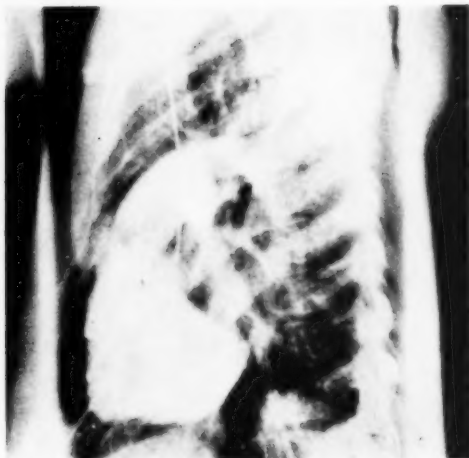
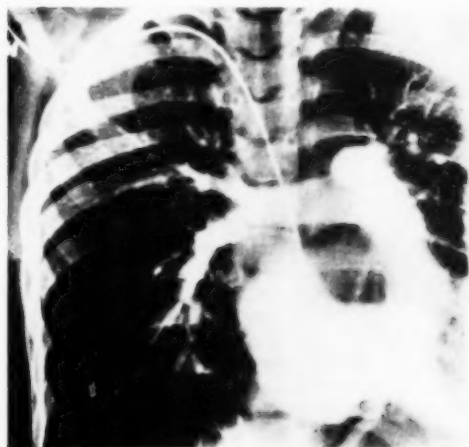


Fig. 2.

Curve from the right ventricle in a case of severe funnel chest and deformed thorax (case No. 19). Diastolic plateau and dip.



Figs. 3 a and b.

Angiocardiography from patient No. 18 showing the dislocation of the heart.

Illustrations to ABDOMINAL AORTOGRAPHY on the following pages

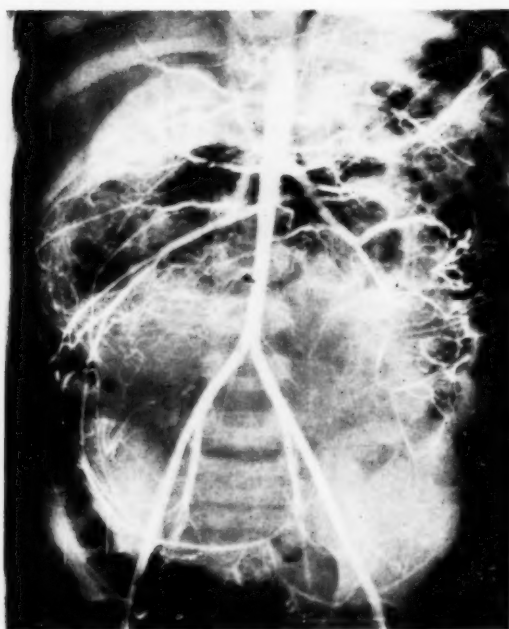


Fig. 1.

Retroperitoneal sarcoma.

The superior mesenteric artery and its branches are displaced by the large tumour, while the clearly filled renal arteries and the weakly delineated nephrograms show normal conditions.

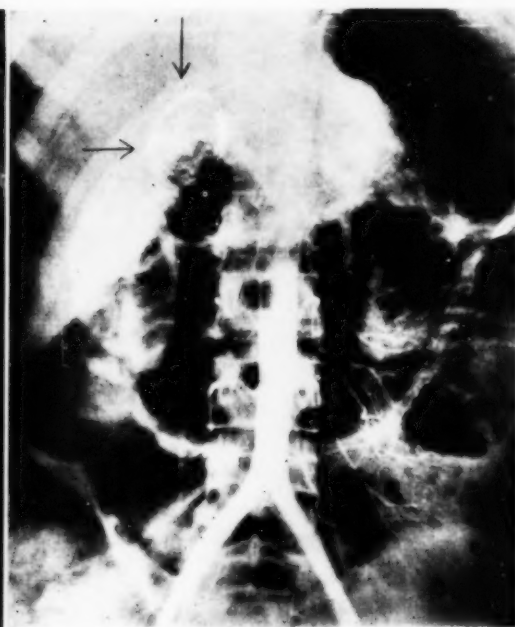


Fig. 2.

Pheochromocytoma.

A large glomerule is seen originating from the right suprarenal artery, in the region of the right suprarenal.

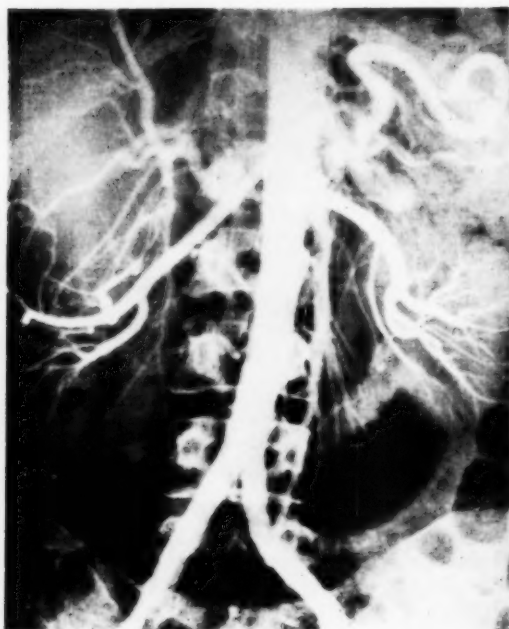


Fig. 3.

Hypernephroma.

- a. Arterial phase. Right renal artery seen displaced inferiorly. b. Nephrogram. Accumulation of contrast medium seen in the tumour vessels.

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References:

- Albrechtsen, S. R.: *Ugeskr. Læger* 1954, 116: 905.
 Brodtkin, H. A.: *Am. J. Surg.* 1948, 75: 716.
 Dressler, W. & H. Roesler: *Am. Heart J.* 1950, 40: 877.
 Edling, N. P. G.: *Acta Radiol.* 1953, 39: 273.
 Ernberg, T.: *Acta Med. Scand.* 1951, suppl. 262: 51.
 Evans, W.: *Brit. Heart J.* 1946, 8: 162.
 Hansen, A. T., P. Eskildsen & H. Gøtzsche: *Circulation* 1951, 3: 881.
 Lester, C. W.: *J. Thor. Surg.* 1950, 19: 507.
 Lindskog, G. E. & W. L. Felton: *Surg. Gyn. & Obst.* 1952, 95: 615.
 Master, A. M. & J. Stone: *Am. J. Med. Sc.* 1949, 217: 392.
 Myhre, J. R.: *Nord. Med.* 1955, 53: 150.
 Ravitch, M. M.: *Surgery* 1951, 30: 178.
 Roesler, H.: *Am. J. Roentgenol.* 1934, 32: 464.
 Therkelsen, F.: *Nord. Med.* 1953, 49: 281.
 Wachtel, F. W., M. M. Ravitch & A. Grishman: *Am. Heart J.* 1956, 52: 121.

ABDOMINAL AORTOGRAPHY IN DISEASES OF THE KIDNEYS AND ADRENALS

By PER DAMGAARD-MØRCH, OLAF PETERSEN and ERIK SANDØE

Dos Santos, Lamas & Caldas were the first, in 1929, to provide a practicable technique of abdominal aortography, and at the same time pointed out the great significance such an examination could have for diagnosing diseases of the kidneys.

Later, numerous studies appeared on the use of the method, both in the examination of patients with kidney disease (Dos Santos 1937, Runstrøm 1948, Weyde 1948, 1951, 1952 and 1954, Denstad 1952, and many others), and in demonstrating tumours of the adrenals (Roux-Berger et al., 1934, Bannick et al., 1939, Koonce et al., 1952, Peirce 1953, Goodwin et al., 1955, Snyder et al., 1955, and others).

The first Danish reports on the subject appeared in 1954 (Eltorm et al., Thomsen et al., and Trautner et al.). Thus, in their work from the radiological department and medical department B of the Rigshospital, Thomsen & Tybjærg Hansen have given an account of the results of 32 abdominal aortographies, 21 of which have been carried out on patients referred for observation for kidney disease. The method has been used regularly since then in the work of the two departments, and we are now able to report on the findings and complications in a total of 68 abdominal aortographies, carried out on patients who were either referred because of suspected kidney disease (59 cases) or for observation for an adrenal tumour (9 cases).

Method and Technique:

In three cases, the injection of the radiopaque dye was made by the translumbar route, accord-

ing to Dos Santos' method. In the remainder of the patients, the contrast material was injected through a catheter, introduced by the transfemoral route. A polyethylene catheter approximately 70 cm long was used, with an outer diameter of 2 mm and an inner diameter of 1.6 mm, introduced into the femoral artery by a modified Seldinger technique (Thomsen & Tybjærg Hansen, 1954). In all cases, an attempt was made to place the tip of the catheter on the level of the intervertebral disk between the 1st and 2nd lumbar vertebrae. As the polyethylene catheter is not opaque to X-rays, it was necessary to inject a little contrast medium in order to determine the position on the trial exposure.

In the majority of cases, the injection was carried out by means of a metal syringe with a lever arrangement to produce high pressure (Jønsen, 1949). At first, approximately 60 ml contrast medium was used in each examination, but this was very quickly reduced to only 20—30 ml. per injection. The injection usually lasted for 2—3 seconds. In 52 cases, the radiopaque dye used was diodone, in 11 cases diatinol, in 4 cases diodrast and in one case umbradil. The strength of the solution varied from 50 per cent up to 70 per cent. During the injection, the patients were under full anaesthesia in all cases (pentothal-curacit).

In the first two aortographies the cassette was changed manually, while in the remainder an automatic film changer was used. A rather varying exposure frequency and number of exposures have been used in the course of time. The procedure now followed, and the one we believe gives the best results, is 2 pictures per second for 5 seconds, followed by 1 picture per second for 5 seconds and 1 picture per 10 seconds for a further 50 seconds, to illustrate both the arteriogram phase and the nephrogram phase, and then 5 minutes later one more exposure to obtain a repro-

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duction of the maximum pyelogram effect. Varying according to the thickness of the soft tissues, 90—100 kV, 320—350 mA and exposure times from 0.014 to 0.05 seconds have been used.

Complications:

Following an abdominal aortography in a woman of 36 years of age, a severe paresis of the lower extremities and disturbances in the function of the sphincter of the bladder occurred, and on examination 5 years later, the neurological symptoms had remained of the same degree of severity. In 4 other patients of respectively 30, 40, 65 and 11 years of age, oliguria appeared after the aortography, and a blood urea rise of up to 270 mg per 100 ml. The conditions became normal after a week, and in none of the cases does the examination appear to have caused any permanent reduction in the kidney function. In the patient who developed signs of severe neurological deficit after the aortography, 20 ml of 50 per cent diarginol had been injected, while in the last four cases mentioned, 60 ml of 70 per cent diodone, 40 ml of 70 per cent diodone, 20 ml of 50 per cent diarginol and 15 ml of 50 per cent diodone respectively had been used.

In the translumbar technique, no complications were observed which could be directly ascribed to the puncture, whereas at the start, when the original Seldinger technique was employed, and a spiral spring used as a guide in the insertion of the polyethylene catheter, a couple of unpleasant complications were seen in the transfemoral method. As described by Thomsen & Tybjærg Hansen (1954), in one case the point of the spring perforated the wall of the vessel and broke off in the periarterial tissue, while in the other case it became bent and stuck fast in the needle. After changing over to a thick nylon stiletto or a Courland catheter No. 4 stiffen-

ed by a metal stiletto the insertion of the polyethylene catheter caused no difficulty.

Results:

The diagnostic results of the 68 abdominal aortographies are summed up in Table 1. In the same table, the operative findings are given for those of our patients who were later operated on, in all 26.

Three patients had a retroperitoneal sarcoma. In these cases, the aortography showed a slightly dislocated but otherwise completely normal arteriogram and nephrogram lying beside the tumour shadow demonstrated (see Fig. 1). In two patients with phæochromocytoma, a delicately threaded glomerule, originating from one of the branches of the suprarenal artery, was clearly seen on one side in the adrenal region (Fig. 2).

The renal tumours were demonstrated partly as a result of their deforming the arteriogram, partly by their delineation in the nephrogram, where in some cases they showed their presence as unclearly delimited regions of contrast retention in large tortuous vessels (see Fig. 3), and in other cases as one or more roundish defects without delineation of the vessels. The former appearance was observed in 6 patients, and in all of them a hypernephroma was found on subsequent operation. The latter appearance was found in three cases. In two of them, it was thought to be a question of cysts of the kidney, in the third, the clinical examination gave rise to a suspicion of malignant disease; the patient was operated on, and a sarcoma of the kidney was found.

The nephrogram also gave good information on the form and size of the kidneys. Thus, in four cases a hydronephrosis was found, in three cases a fused kidney (see Fig. 4), and in one case a fused kidney complicated by a hydronephrosis.

Table 1.

Diagnosis on abdominal aortography		Number of patients operated on later		Findings on operation	
Retroperitoneal tumour	3	3	Retroperitoneal sarcoma	1	3
Phæochromocytoma	2	2	Phæochromocytoma	1	2
Vascular kidney tumour	6	5	Hypernephroma	1	5
Vascular kidney tumour and fused kidney	1	1	Hypernephroma and fused kidney	1	1
Renal tumour without delineation of vessels	3	1	Renal sarcoma	1	1
Hydronephrosis	4	2	Hydronephrosis	1	2
Fused kidney	3	3	Fused kidney	1	3
Fused kidney and hydronephrosis	1	1	Fused kidney and hydronephrosis	1	1
Lobulated kidney	1	1	Lobulated kidney	1	1
Hypoplasia of right kidney	1	0			
Reduced nephrogram effect on the one side	4	3	Pelvic cancer	1	1
			Pyelonephritic dwarf kidney	1	2
Unilateral aplasia of kidney	4	0			
Hydronephrosis or renal cyst	1	1	Hydronephrosis	1	1
Supernumerary renal arteries	4	1	Normal kidneys with normal vessel supply	1	1
Nothing abnormal	30	2	Nothing abnormal	1	1
			Renal cyst	1	1

Survey of the diagnostic yield in 68 abdominal aortographies. On the right of the table the operational findings are inserted for the 26 patients who later were operated on for their kidney or adrenal disease.

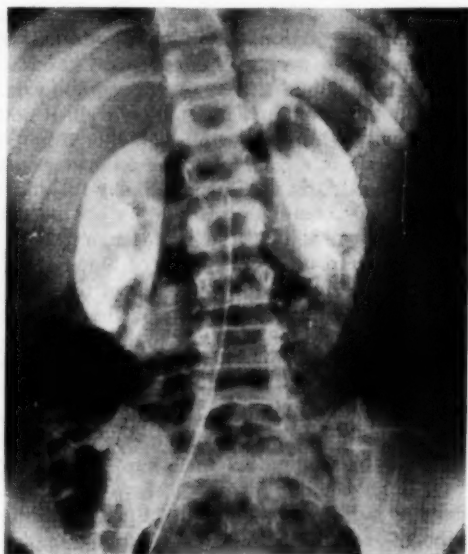


Fig. 4.
A fused kidney.
Nephrogram phase.

Minor anomalies, such as lobulations of the kidney and hypoplasia of the one kidney, were revealed in a further two cases. In four patients, a reduced nephrogram effect has been demonstrated on the one side. Three of them were operated on: in two of them, a pyelonephritic contracted kidney was found, and in the third one a pelvic cancer, which had grown into the kidney parenchyma and completely infiltrated it.

In four cases, no delineation of the kidney artery and completely abolished nephrogram and pyelogram effect was observed on one side. This finding was taken as supporting the diagnosis of unilateral aplasia of the kidney, and none of the patients was operated on. In one further case, it was impossible to observe the filling of the renal artery, but later during the examination of this patient a rounded contrast shadow, the size of a baby's head, was seen in the place of the kidney. It was considered to be a case of either hydronephrosis or a large kidney cyst, and that the non-filling of the renal artery was due to secondary degenerative changes. On operation, a large hydronephrosis was found.

In several of the patients, apparently more than one artery to the same kidney was found, and in one it was considered likely that the symptoms present were due to the aberrant vessel demonstrated. The patient was operated on, but the operation was unable to show anything abnormal in the vessel supply to the kidney. A renewed examination of the aortogram led to the conclusion that, in spite of all, the patient must have an aberrant vessel to the one kidney pole, and

that was impossible to give any explanation of the negative operational findings.

In one further case, there was a discrepancy between the findings of the aortography and those on operation later. This concerned a patient whose arteriogram and nephrogram had shown normal conditions, but where the urography had aroused a strong suspicion that a tumour was present in the inferior pole of the kidney on the one side. In spite of the negative findings in the arteriogram, it was decided to operate, and a cyst as large as a hen's egg was found localized as expected.

Of the remaining 33 patients, in whom the aortography showed normal conditions or simply a supernumerary kidney artery, the 26 were referred for observation for a kidney tumour, the 6 for a phaeochromocytoma and the last one for a suspected tumour of the adrenal cortex.

If the diagnostic gains in respectively intravenous urography and abdominal aortography are compared, it appears, by using the latter method, that it was easier to decide whether a tumour was renal or extra-renal in origin, that it was possible to distinguish a hypernephroma from the other kidney tumours with greater certainty, and that the reason for unilateral excretion in the urography could be cleared up in several cases. Finally, in four patients whose pyelograms gave no hint whatever of the presence of a tumour, a hypernephroma could be demonstrated in two and a phaeochromocytoma in the other two. On the other hand, a definitely deformed pyelogram but a completely normal arteriogram and nephrogram were found in a patient who on operation turned out to have a cyst of the kidney.

7 of the 9 patients who were referred for observation for tumour of the kidney had previously been examined radiologically after retroperitoneal insufflation of air, without anything definitely abnormal having been observed. This was also the case with the two patients where it had been possible to demonstrate a phaeochromocytoma by means of aortography.

DISCUSSION

Nowadays, radiopaque substances containing organically bound iodine are used in most places. In spite of this, there are still reports of serious complications in abdominal aortography. These are first and foremost cases of renal damage (Larsson et al., 1952, Thomsen et al.*), 1954, Johnsson et al., 1954, Miller et al., 1954, Josselson et al., 1954, McAfee et al.,

* Thomsen & Tybjaerg Hansen mention three cases of kidney damage after abdominal aortography. Two of these arose in patients referred for investigation for vascular disease, and have therefore not been included in our material.

1956, Berg 1956, and others), the majority being transient, some few with a permanent depression of kidney function as a sequel, and a very few cases with a fatal outcome. Next, some cases of severe paresis of the lower extremities have been described (Antoni et al., 1949, Boyarsky 1954, Abeshouse 1956, Baurys 1956 and McCarmac 1956), and a single case of pancreatitis (Robinson 1957). Finally, in two cases of patients with phæochromocytoma, it has been reported that the abdominal aortography released a fatal hypertensive crisis (Koonce et al., 1952, Saltz et al., 1956). As mentioned, in our own material we had one abdominal aortography complicated by a paresis of the lower extremities, and four which involved transient kidney damage.

A few of the complications reported can be due to the fact that all the contrast was injected directly into one of the renal arteries (Miller et al. 1954, McAfee et al. 1956), or into the coeliac artery (Robinson, 1957). This state of affairs has only been found where the translumbar puncture technique has been used, and never in patients where the contrast medium was injected by the transfemoral route, as in this case there has always been the possibility of controlling the position of the catheter by means of a test exposure, before carrying out the abdominal aortography. In others, relatively large amounts of contrast have been used (among these patients might be mentioned two of ours who developed transient oliguria and blood urea elevation). However, in the majority of the cases referred to, the injection of the contrast medium has taken place in the normal manner into the abdominal aorta, and the amount of contrast material has not exceeded the 20–30 ml required to obtain adequate filling of the vessels of the kidneys and adrenals. It appears, therefore, that with our present technique, it is impossible wholly to avoid serious complications in abdominal aortography.

Recently, methods have been published by Swedish authors (Edholm & Seldinger, 1956, Tillander, 1956 and Ödmann, 1956) for a so-called selective aortography, which should make it possible to inject the contrast directly into the artery of the organ to be examined. It should thereby be possible to reduce the contrast dose considerably, and completely avoid damage to the remaining abdominal organs and to the spinal chord, just as a possible damage to the kidneys ought never to have catastrophic sequelae, when only one kidney comes into contact with the contrast material. If the selective aortography lives up to its promise, it will undoubtedly be the method of choice in the future.

With our present technique, however, we must conclude that in individual rare cases abdominal aortography can involve very severe complications, and should therefore only be used when the diagnostic possibilities of other and less

dangerous methods of examination are exhausted. If there is a suspicion of kidney or adrenal disease, intravenous urography ought first to be carried out, and should this show incomplete excretion, then retrograde pyelography as well. If nothing abnormal is hereby demonstrated, or if no certain diagnosis is reached, abdominal aortography may be indicated. It will be possible by this means to obtain very complete information on the position, size, form and degree of vascularization of the kidneys and on their supply of blood vessels, together with the possible presence of tumours in the renal or adrenal regions. In particular, aortography will make it possible to distinguish between renal and extrarenal tumours, to identify a hypernephroma among the other renal tumours, and to either invalidate or support the diagnosis of unilateral aplasia of the kidney. In addition, it appears that abdominal aortography is superior to all other methods when it is a question of localizing a phæochromocytoma. Finally, it should be borne in mind that, even in the case of patients with relatively large kidney tumours, one can in rare instances see normal arteriograms and nephrograms.

One would always hesitate to carry out an abdominal aortography in patients with reduced kidney function, as in such cases even minor kidney damage might have disastrous consequences. On the other hand, abdominal aortography in some of these patients can give very valuable information, so that in each particular case it is necessary to consider very carefully whether the benefits which the patient might gain by a further clarification of the nature of his kidney disease balance the risk he runs from the examination. In this connection, it might be mentioned that Trautner & Pahle (1954), without complications of any kind, carried out an abdominal aortography on a 23-year old woman, who had had complete anuria for 6 days as a result of a bilateral cortical necrosis.

SUMMARY

A survey is made of the results and complications in a total of 68 cases of abdominal aortography, carried out on patients referred for observation for disease of the kidneys or tumour of the adrenals. The technique in the procedure is discussed. It is concluded that abdominal aortography gives very valuable information, which it is often not possible to obtain otherwise, on the presence of tumours in the kidneys or adrenals, together with the form and size of the kidneys and their supply of blood vessels. In particular, the great significance of the method for the localization of phæochromocytomas is mentioned. On the other hand, it is stressed that in rare cases, abdominal aortography can cause serious complications. Such a case is found in the present material, where paresis of the lower extremities developed following on the examination. Ab-

dominal aortography should therefore only be employed when the diagnostic possibilities of other and less risky methods of examination have been completely exhausted.

References:

- Abeshouse, B. & A. Tjongson: J. Urol. 1956, 75: 348.
Antoni, N. & E. Lindgren: Acta chir. scandinav. 1949, 96: 230.
Bannick, E. & O. Nelson: Goodwin ref.
Baurys, W.: J. Urol. 1956, 75: 846.
Berg, O.: South. M. J. 1956, 49: 497.
Boyarsky, S.: JAMA 1954, 156: 599.
McCormac, J.: JAMA 1956, 161: 860.
Denstad, T.: Acta radiol. 1952, 38: 187.
Edholm, P. & S. Seidinger: Acta radiol. 1956, 45: 15.
Elltorm, H., A. Gammelgaard & O. Tarp: Ugeskr. Læger, 1954, 116: 375.
Goodwin, W., E. Moore & E. Peirce: J. Urol. 1955, 74: 231.
Johansson, S. & T. Normann: Nord. Med. 1954, 52: 1188.
Josselson, A. & J. Kaplan: J. Urol. 1954, 72: 256.
Jönsson, G.: Acta radiol. 1949, 31: 376.
Koonce, D., B. Pollock & Z. Glassy: Am. Heart J. 1952, 44: 901.
Larsson, H. & A. Palmlov: Acta radiol. 1952, 38: 111.
McAfee, J. & J. Wilson: Am. J. Roentgenol. 1956, 75: 956.
Miller, G., E. Wyllie & F. Hinman: Surgery 1954, 35: 885.
Peirce, E.: J. Internat. Coll. Surgeons 1953, 20: 16.
Robinson, A.: Arch. Surg. 1956, 72: 290.
Roux-Berger, J., J. Naulleau & X. Contiades: ref. Goodwin.
Runström, G.: Nord. Med. 1948, 38: 934.
Saltz, N., E. Luttwak, A. Schwartz & G. Goldberg: Ann. Surg. 1956, 144: 118.
dos Santos, R., A. Lamas & J. Caldas: Bull. et mém. Soc. Nat. chir. 1929, 55: 587.
dos Santos, R.: J. internat. chir. 1937, 2: 609.
Snyder, C. & J. Rutledge: Pediatrics 1955, 15: 312.
Thomsen, G. & A. Tybjerg Hansen: Ugeskr. Læger 1954, 116: 369.
Trautner, K. & H. Pahle: Ugeskr. Læger 1954, 116: 381.
Tillander, H.: Acta radiol. 1956, 45: 21.
Weyde, R.: Nord. Med. 1948, 38: 1228, 1951, 45: 97, 1952, 47: 212 & Radiol. Clinic, Basel, 1954, 23: 313.
Ödmann, Per: Acta radiol. 1956, 45: 1.

SUBJECT INDEX

- Abdominal aortography in diseases of the kidneys and adrenals** 257
- ABO blood group. Peptic ulcer and the — system** 45
- Accident. Deaths by — among children in Denmark 1931—1955** 219
- Accidents. A statistical analysis of —** 230
- Acidosis. The treatment of respiratory —** 47
- ACTH. Non-reactive miliary tuberculosis and moniliasis complicating severe granulocytopenia treated with — and cortisone** 147
- Actocortin** 200
- Adrenals. Abdominal aortography in diseases of the kidneys and —** 257
- Adults. Isolation of Echo virus from two cases of "minor illness" in —** 236
- Aetiology. The — of primary varicose veins** 102
- Amaurotic idiocy. Lymphocyte degeneration in —** 156
- Anaemia. Haemolytic — in Denmark** 141
- **Auto-immune haemolytic —** 143
- **in Hodgkin's disease and chronic lymphatic leukaemia** 150
- Aorta. Coarctation of the —** 33
- Aortography. Abdominal — in diseases of the kidneys and adrenals** 257
- Arteriography. Thrombosis of the internal carotid artery verified by —** 240
- Artificial respiration. The employment of — in diseases other than poliomyelitis** 9
- Autocatalytic reaction. The — in blood coagulation** 160
- Auto-immune haemolytic anaemia** 143
- B CG-vaccination. The efficacy of —** 13
- Blood coagulation. Defects in —** 164
- **coagulation. The autocatalytic reaction in — group. Peptic ulcer and the ABO — system** 45
- **group. The Lewis — Lea in adults** 210
- Cancer incidence in Denmark 1943 to 1953. IV. —** 55
- **Total gastrectomy and construction of jejunal reservoir in the treatment of advanced gastric —** 201
- **Transverse colon as a substitute for the stomach following total gastrectomy for —** 205
- Carcinoid. Metastasizing — and 5-hydroxytryptamine** 96
- Carcinoma. Diffuse scirrous —** 93
- Cardiac function in funnel chest** 251
- Carotid artery. Thrombosis of the internal — verified by arteriography** 240
- Cerebrospinal fluids. Isolation of Echo virus type 9 from —** 233
- **fluid. Uric acid in the —** 22
- Children. Deaths by accident among — in Denmark 1931—1955** 219
- Chlorpromazine. Diabetes mellitus in a psychotic patient with recovery during — therapy** 134
- Cholangiography. Operative —** 113
- Cholinergic crises in the treatment of myasthenia gravis** 126
- Classification of diseases. The — in general practice** 183
- Climacterium. Surgical —** 111
- Coarctation of the aorta** 33
- Colon. Transverse — as a substitute for the stomach following total gastrectomy for cancer** 205
- Complement. Fixation of thermolabile serum globulin — to sensitized red blood cells** 137
- Conservative and hemodialytic treatment of acute renal failure.** 73
- Cortisone. Non-reactive miliary tuberculosis and moniliasis complicating severe granulocytopenia treated with ACTH and cortisone** 147
- Danish Medical Association. Centenary of the —** 169
- Deaths by accident among children in Denmark 1931—1955** 219
- Defects in blood coagulation** 164
- Degeneration. Lymphocyte — in amaurotic idiocy** 156
- Denmark. Cancer incidence in — 1943 to 1953. IV.** 55
- **Deaths by accident among children in — 1931—1955** 219
- **Haemolytic anaemia in —** 141
- **The development of Medicine in — since the foundation of the University of Copenhagen in 1479** 170
- **The incidence of pulmonary tuberculosis in — by sex and age 1921—1955** 191
- Dermatomyositis and tumor** 196
- Development The — of Medicine in Denmark since the foundation of the University of Copenhagen in 1479** 170
- Diabetes mellitus in a psychotic patient with recovery during chlorpromazine therapy** 134
- Disease. Bilateral polycystic — of the kidneys** 128
- Diseases. Abdominal aortography in — of the kidneys and adrenals** 257
- **The classification of — in general practice** 183
- Dumping syndrome. Investigations concerning the pathogenesis of the —** 208
- Echo virus. Isolation of — from two cases of "minor illness" in adults** 236
- **Isolation of — type 9 from cerebrospinal fluids** 233
- Endoscopies. Pethidine for —** 16
- Fibrinolytic effects. Partial purification and — of a factor in peptone** 159
- Foetal growth. Correlation between human — and water and protein contents of maternal tissues and body fluids** 26
- Funnel chest. Cardiac function in —** 251
- Gastrectomy. Total — and construction of jejunal reservoir in the treatment of advanced gastric cancer** 201
- **Transverse colon as a substitute for the stomach following total — for cancer** 205
- General practice. Morbidity statistics from —** 190
- **The classification of diseases in —** 183
- Genital prolapse. Surgical treatment of —** 121
- Granulocytopenia. Non-reactive miliary tuberculosis and moniliasis complicating severe — treated with ACTH and cortisone** 147
- Gynaecomastia in Hodgkin's disease** 157
- Hemodialytic treatment. Conservative and — in acute renal failure** 73
- Haemolytic anaemia in Denmark** 141
- **Auto-immune —** 143
- Hodgkin's disease. Anaemia in — and chronic lymphatic leukemia** 150
- **Gynaecomastia in —** 157
- Hospital. The role of the — in the public health programme** 179
- Hydroxytryptamine. Metastasizing carcinoid and —** 96
- Hypo-gammaglobulinanaemia. Recurrent pneumonia in multiple myeloma due to acquired functional —** 153

Idiocy. Lymphocyte degeneration in amaurotic —	156	Psycho-sexual relations in surgical climacterium	111
Incidence. Cancer — in Denmark 1943 to 1953. IV.	55	Public health. The role of the hospital in the —	179
— The — of pulmonary tuberculosis in Den-	191	Pulmonary tuberculosis. The incidence of — in	191
mark by sex and age 1921—1955	248	Purification. Partial — and fibrinolytic effect of	159
Infarction. Serum glutamic oxalacetic transamin-	18	a factor in peptone	
ase in myocardial —	6	Red blood cells. Fixation of thermolabile serum	137
Insulin. Studies on a new long-acting — zinc	236	globulin (complement) to sensitized —	73
methylalbumin insulin	233	Renal failure. Acute —	
Iodine. Protein-bound — in patients operated	201	Respiration. The employment of artificial — in	9
upon for thyrotoxicosis	128	diseases other than poliomyelitis	47
Isolation of Echo virus from two cases of "minor	257	Respiratory acidosis. The treatment of —	
illness" in adults	18		
— type 9 from cerebrospinal fluids	210		
		S cirrouis carcinoma. Diffuse —	93
Jejunal reservoir. Total gastrectomy and con-	219	Sequelae of sterilisation tubarum	107
struction of — in the treatment of advanced	164	Serum globulin. Fixation of thermolabile —	
gastric cancer	55	(complement) to sensitized red blood	137
Kidneys. Abdominal aortography in diseases of	219	cells	248
the — and adrenals	141	— glutamic oxalacetic transaminase in myo-	230
cardial infarction		cardiac infarction	107
		Statistical analysis. A — of accidents	121
Leukemia. Anaemia in Hodgkin's disease and	170	Surgical treatment of genital prolapse	
chronic lymphatic —	191		
Lewis blood group. The — Lea in adults	196		
Long-acting insulin. Studies on a new — zinc	170		
methylalbumin insulin	191		
Lymphatic leukemia. Anaemia in Hodgkin's dis-	196		
ease and chronic —			
Lymphocyte degeneration in amaurotic idiocy ..	170		
		Therapy. Diabetes mellitus in a psychotic patient	134
Medicine. The development of — in Denmark	134	with recovery during chlorpromazine —	
since the foundation of the University of Cop-	128	Thrombosis of the internal carotid artery verified	240
penhagen in 1479	128	by arteriography	
Metastizing carcinoid and 5-hydroxytryptamine	170	Thyrotoxicosis. Operative treatment of —	
Miliary tuberculosis. Non-reactive — and moni-	96	I. Primary results	1
liasis complicating severe granulocytopenia	170	II. Follow-up	4
treated with ACTH and cortisone	147	— Protein-bound iodine in patients operated	6
Minor illness. Isolation of Echo virus from two	208	upon for —	217
cases of — in adults	236	— Polyradiculo-myopathia in transient —	
Mitral disease. Transbronchial pressure measure-	51	Transaminase. Serum glutamic oxalacetic — in	248
ments in the left auricle in the diagnosis of —	51	myocardial infarction	
Moniliasis. Non-reactive miliary tuberculosis	233	Transbronchial pressure measurement in the left	51
and — complicating severe granulocytopenia	16	auricle in the diagnosis of mitral disease	
treated with ACTH and cortisone	147	Treatment. Cholinergic crises in the — of mya-	126
Morbidity statistics from general practice	190	sthenia gravis	
Myasthenia gravis. Cholinergic crises in the treat-	126	— Conservative and hemodialytic — in acute	73
ment of —	126	renal failure	
Myocardial infarction. Serum glutamic oxalacetic	248	— Operative — of thyrotoxicosis.	
transaminase in —	153	I. Primary results	1
Myeloma. Recurrent pneumonia in multiple —	201	II. Follow-up	4
due to acquired functional hypo-gammaglobu-	201	— Surgical — of genital prolapse	121
lin-aemia	113	— The — of respiratory acidosis	47
Operative cholangiography	205	— Total gastrectomy and construction of	
Operative treatment of thyrotoxicosis.	190	jejunal reservoir in the — of advanced	201
I. Primary results	183	gastric cancer	
II. Follow-up	121	Tuberculosis. Non-reactive miliary — and moni-	147
		liasis complicating severe granulocytopenia	
Pathogenesis. Investigations concerning the — of	147	treated with ACTH and cortisone ..	
the dumping syndrome	208	— The incidence of pulmonary — in Den-	191
Peptic ulcer and the ABO blood group system ..	45	mark by sex and age 1921—1955	196
Peptone. Partial purification and fibrinolytic	159	Tumor. Dermatomyositis and —	
effect of a factor in —	16		
Pethidine for endoscopies	73		
Pneumonia. Recurrent — in multiple myeloma	141		
due to acquired functional hypo-gammaglobu-	143		
lin-aemia	150		
Polycystic disease. Bilateral — of the kidneys ..	157		
Polyradiculo-myopathia in transient thyrotoxi-	179		
cosis	96		
Pressure measurements. Transbronchial — in the	153		
left auricle in the diagnosis of mitral disease ..	121		
Prolapse. Surgical treatment of genital —	6		
Protein-bound iodine in patients operated upon	26		
for thyrotoxicosis			
Protein content. Correlation between human foetal			
growth and water and — content of maternal			
tissues and body fluids			
		University of Copenhagen. The development of	
		Medicine in Denmark since the foundation of	
		the — in 1479	170
		Uric acid in the cerebrospinal fluid	22
		Varicose veins. The aetiology of primary —	102
		Veins. The aetiology of primary varicose —	102
		Virus. Isolation of Echo — from two cases of	
		"minor illness" in adults	236
		— Isolation of Echo — type 9 from cerebro-	233
		spinal fluids	
		Water and protein content. Correlation between	
		human foetal growth and — of maternal tissues	26
		and body fluids	
		Z inc methylalbumin insulin. Studies on a new	18
		long-acting insulin —	

INDEX OF AUTHORS

Amdrup, E.	208	Jordal, Kell	210
Andersen, Ib	51	Jordal, Robert	196
Andersen, Jørgen	137	Jørgensen, Mogens	51
Andreassen, Mogens	201		
Arnoldi, Carl C.	102	Killmann, Sven-Age..	73, 153
Astrup, Tage	159, 160, 164	Knudsen, Else Ehlert	153
		Kristensen, H. K.	16
Bach-Nielsen, P.	121		
Balslev-Jørgensen, J.	208	Laursen, Thomas	248
Berthelsen, Helge G.	107	Letman, Henning	141, 143
Bichel, Jørgen	157	Lorenzen, Jørgen	134
Birket-Smith, E.	217	Lyng, J.	200
Bisgaard, Ingeborg Maack	147		
		Magnus, Herdis von	233
Castberg, Thomas	113	Mosekilde, Eyvind	113
Clemmesen, Johannes	55		
Crone, Christian	22	Nielsen, Arne	55
		Nørregaard, Svend A.	219
Dahlerup, Jens Vilh.	183		
Dalgaard, Ole Z.	128	Olesen, E. S.	159
Damgaard-Mørch, Per	257	Olesen, Ove Lykke	33
Davidsen, H. Gösta	251	Olivarius, Bent de Fine	217
Dreyer, Karen	219		
Dyrberg, V.	47	Paaby, P.	26
		Pedersen, A. Leth	111
Eskildsen, P.	51	Petersen, Helge	126
		Petersen, Knud Birkum	236
Fabricius, J.	251	Petersen, Olaf	257
Fischermann, Kaj	93	Plum, Claus Munk	156
Frandsen, Johannes	179	Poulsen, Thue	51
Friis, Th.	1, 4, 6		
Fuchs, Fritz	1, 4, 6	Remvig, Jørgen	134
		Ruben, H.	16
Gammeltoft, A.	16		
Gjørup, Steffen	73	Sandøe, Erik	257
Godtfredsen, Annelise	233	Sjolin, Knud-Erik	164
Gormsen, J.	47	Skensved, Ole	18
Gotfredsen, Edvard	170	Skjelboe, B.	205
		Skinhøj, Erik	126, 240
Hansen, A. Tybjærg	251	Stakemann, Georg	121
Hansen, P. From	248	Stenderup, A.	147
Hansen, T. Svend	1, 4, 6	Sørensen, K. Harry	45
Henriksen, Erik	9		
Hyge, Tage V.	13	Thaysen, Jørn Hess	73
Iversen, Erik	191	Unger, M. O.	200
Iversen, Kurt	1, 4, 6		
		Vermehren, Emil	200
Jacobsen, Hans-Henrik	240	Vermehren, Martin	200
Jensen, Kaj Bjørn	150	Weibüll, T.	200
Jensen, Klaus	96		
Jensenius, Hans	230	Zacho, A.	205
Johansen, S. H.	16, 47		

210
 196
 51
 153
 153
 16
 248
 143
 134
 200
 233
 113
 55
 219
 156
 33
 217
 26
 111
 126
 236
 257
 156
 51
 134
 16
 257
 164
 16
 206
 6, 240
 121
 147
 45
 73
 200
 200
 200
 200
 206